

Section 1 Introduction to Cardiovascular Disorders

243 Approach to the Patient with Possible Cardiovascular Disease

Joseph Loscalzo

■ THE MAGNITUDE OF THE PROBLEM

Cardiovascular diseases comprise the most prevalent serious disorders in industrialized nations and are a rapidly increasing problem in developing nations (Chap. 245). Age-adjusted death rates for coronary heart disease have declined by two-thirds in the past four decades in the United States, reflecting the identification and reduction of risk factors as well as improved treatments and interventions for the management of coronary artery disease, arrhythmias, and heart failure. Nonetheless, cardiovascular diseases remain the most common causes of death, responsible for nearly 700,000 deaths each year. Approximately one-third of these deaths are sudden. In addition, cardiovascular diseases are highly prevalent, diagnosed in nearly half of the adult population. The growing prevalence of obesity (Chap. 414), type 2 diabetes mellitus (Chap. 415), and metabolic syndrome (Chap. 420), which are important risk factors for atherosclerosis, now threatens to reverse the progress that has been made in the age-adjusted reduction in the mortality rate of coronary heart disease. Globally, the impact of cardiovascular diseases is steadily mounting, with an estimated 19 million deaths worldwide.

For many years, cardiovascular disease was considered to be more common in men than in women. In fact, cardiovascular disease is the leading cause of all deaths among women and men (Chap. 410). In addition, although the absolute number of deaths secondary to cardiovascular disease has declined over the past decades in men, this number has actually risen in women. Inflammation, obesity, type 2 diabetes mellitus, and the metabolic syndrome appear to play more prominent roles in the development of coronary atherosclerosis in women than in men. Coronary artery disease (CAD) is more frequently associated with dysfunction of the coronary microcirculation in women than in men. Exercise electrocardiography has a lower diagnostic accuracy in the prediction of epicardial obstruction in women than in men.

■ NATURAL HISTORY

Cardiovascular disorders often present acutely, as in a previously asymptomatic person who develops an acute myocardial infarction (Chap. 286), or a previously asymptomatic patient with hypertrophic cardiomyopathy (Chaps. 266–270) or with a prolonged QT interval (Chap. 259) whose first clinical manifestation is syncope or even sudden death. However, the alert physician may recognize the patient at risk for these complications long before they occur and often can take measures to prevent them. For example, a patient with acute myocardial infarction will often have had risk factors for atherosclerosis for many years. Had these risk factors been recognized, their elimination or reduction might have delayed or even prevented the infarction. Similarly, a patient with hypertrophic cardiomyopathy may have had a heart murmur for years and a family history of this disorder. These findings could have led to an echocardiographic examination, recognition of the condition, and appropriate therapy long before the occurrence of a serious acute manifestation.

Patients with valvular heart disease or idiopathic dilated cardiomyopathy, by contrast, may have a prolonged course of gradually increasing dyspnea and other manifestations of chronic heart failure that is punctuated by episodes of acute deterioration only late in the course of

the disease. Understanding the natural history of various cardiac disorders is essential for applying appropriate diagnostic and therapeutic measures to each stage of the condition, as well as for providing the patient and family with the likely prognosis.

■ CARDIAC SYMPTOMS

The symptoms caused by heart disease result most commonly from myocardial ischemia, disturbance of the contraction and/or relaxation of the myocardium, obstruction to blood flow, or an abnormal cardiac rhythm or rate. Ischemia, which is caused by an imbalance between the heart's oxygen supply and demand, is manifest most frequently as chest discomfort (Chap. 15), whereas reduction of the pumping ability of the heart commonly leads to fatigue and elevated intravascular pressure upstream of the failing ventricle. The latter results in abnormal fluid accumulation, with peripheral edema (Chap. 43) or pulmonary congestion and dyspnea (Chap. 39). Obstruction to blood flow, as occurs in valvular stenosis, can cause symptoms resembling those of myocardial failure (Chap. 264). Cardiac arrhythmias often develop suddenly, and the resulting symptoms and signs—palpitations (Chap. 45), dyspnea, hypotension, and syncope (Chap. 23)—generally occur abruptly and may disappear as rapidly as they develop.

Although dyspnea, chest discomfort, edema, and syncope are cardinal manifestations of cardiac disease, they occur in other conditions, as well. Thus, dyspnea is observed in disorders as diverse as pulmonary disease, marked obesity, and anxiety (Chap. 39). Similarly, chest discomfort may result from a variety of noncardiac and cardiac causes other than myocardial ischemia (Chap. 15). Edema, an important finding in untreated or inadequately treated heart failure, also may occur with primary renal disease and in hepatic cirrhosis (Chap. 43). Syncope occurs not only with serious cardiac arrhythmias but in a number of neurologic conditions as well (Chap. 23). Whether heart disease is responsible for these symptoms frequently can be determined by carrying out a careful clinical examination (Chap. 246), supplemented by noninvasive testing using electrocardiography at rest and during exercise (Chap. 247), echocardiography, and cardiopulmonary imaging (Chap. 248).

Myocardial or coronary function that may be adequate at rest may be insufficient during exertion. Thus, dyspnea and/or chest discomfort that appear during activity are characteristic of patients with heart disease, whereas the opposite pattern, that is, the appearance of these symptoms at rest and their remission during exertion, is rarely observed in such patients. It is important, therefore, to question the patient carefully about the relation of symptoms to exertion.

Many patients with cardiovascular disease may be asymptomatic both at rest and during exertion but may present with an abnormal physical finding such as a heart murmur, elevated arterial pressure, or an abnormality of the electrocardiogram (ECG) or imaging test. It is important to assess the global risk of CAD in asymptomatic individuals, using a combination of clinical assessment and measurement of cholesterol and its fractions, as well as other biomarkers, such as C-reactive protein, in some patients. Since the first clinical manifestation of CAD may be catastrophic—sudden cardiac death, acute myocardial infarction, or stroke in previous asymptomatic persons—it is mandatory to identify those at high risk for such events and institute further testing and preventive measures.

■ DIAGNOSIS

As outlined by the New York Heart Association (NYHA), the elements of a complete cardiac diagnosis include the systematic consideration of the following:

1. *The underlying etiology.* Is the disease congenital, hypertensive, ischemic, or inflammatory in origin?
2. *The anatomic abnormalities.* Which chambers are involved? Are they hypertrophied, dilated, or both? Which valves are affected? Are they regurgitant and/or stenotic? Is there pericardial involvement? Has there been a myocardial infarction?

TABLE 243-1 New York Heart Association Functional Classification

Class I No limitation of physical activity No symptoms with ordinary exertion	Class III Marked limitation of physical activity Less than ordinary activity causes symptoms
Class II Slight limitation of physical activity Ordinary activity causes symptoms	Class IV Inability to carry out any physical activity without discomfort Symptoms at rest

3. *The physiologic disturbances.* Is an arrhythmia present? Is there evidence of congestive heart failure or myocardial ischemia?
4. *Functional disability.* How strenuous is the physical activity required to elicit symptoms? The classification provided by the NYHA has been found to be useful in describing functional disability (Table 243-1).

One example may serve to illustrate the importance of establishing a complete diagnosis. In a patient who presents with exertional chest discomfort, the identification of myocardial ischemia as the etiology is of great clinical importance. However, the simple recognition of ischemia is insufficient to formulate a therapeutic strategy or prognosis until the underlying anatomic abnormalities responsible for the myocardial ischemia, for example, coronary atherosclerosis or aortic stenosis, are identified and a judgment is made about whether other physiologic disturbances that cause an imbalance between myocardial oxygen supply and demand, such as severe anemia, thyrotoxicosis, or supraventricular tachycardia, play contributory roles. Finally, the severity of the disability should govern the extent and tempo of the workup and strongly influence the therapeutic strategy that is selected.

The establishment of a correct and complete cardiac diagnosis usually commences with the history and physical examination (Chap. 246). Indeed, the clinical examination remains the basis for the diagnosis of a wide variety of disorders. The clinical examination may then be supplemented by five types of laboratory tests: (1) ECG (Chap. 247); (2) noninvasive imaging examinations (chest x-ray, echocardiogram, radionuclide imaging, computed tomographic imaging, positron emission tomography, and magnetic resonance imaging) (Chap. 248); (3) blood tests to assess risk (e.g., lipid determinations, C-reactive protein) or cardiac function (e.g., brain natriuretic peptide [BNP] [Chap. 264]); (4) occasionally, specialized invasive examinations (i.e., cardiac catheterization and coronary arteriography [Chap. 249]); and (5) genetic tests to identify monogenic cardiac diseases (e.g., hypertrophic cardiomyopathy [Chaps. 266–270], Marfan's syndrome [Chap. 425], and abnormalities of cardiac ion channels that lead to prolongation of the QT interval and an increase in the risk of sudden death [Chap. 253]). These genetic tests are becoming more widely available.

FAMILY HISTORY

In eliciting the history of a patient with known or suspected cardiovascular disease, particular attention should be directed to the family history. Familial clustering is common in many forms of heart disease. Mendelian transmission of single-gene defects may occur, as in hypertrophic cardiomyopathy (Chaps. 266–270), Marfan's syndrome (Chap. 425), and sudden death associated with a prolonged QT syndrome (Chap. 259). Premature coronary disease and essential hypertension, type 2 diabetes mellitus, and hyperlipidemia (the most important risk factors for CAD) are usually polygenic disorders. Although familial transmission may be less obvious than in the monogenic disorders, it is helpful in assessing risk and prognosis in polygenic disorders, as well. Familial clustering of cardiovascular diseases not only may occur on a genetic basis but also may be related to familial dietary or behavior patterns, such as excessive ingestion of salt or calories and cigarette smoking.

ASSESSMENT OF FUNCTIONAL IMPAIRMENT

When an attempt is made to determine the severity of functional impairment in a patient with heart disease, it is helpful to ascertain the

level of activity and the rate at which it is performed before symptoms develop. Thus, it is not sufficient to state that the patient complains of dyspnea. The breathlessness that occurs after running up two long flights of stairs denotes far less functional impairment than do similar symptoms that occur after taking a few steps on level ground. In addition, the degree of customary physical activity at work and during recreation should be considered. The development of two-flight dyspnea in a well-conditioned marathon runner may be far more significant than the development of one-flight dyspnea in a previously sedentary person. The history should include a detailed consideration of the patient's therapeutic regimen. For example, the persistence or development of edema, breathlessness, and other manifestations of heart failure in a patient who is receiving optimal doses of diuretics and other therapies for heart failure (Chap. 264) is far graver than are similar manifestations in the absence of treatment. In an effort to determine the progression of symptoms, and thus the severity of the underlying illness, it may be useful to ascertain what, if any, specific tasks the patient could have carried out 6 months or 1 year earlier that they cannot perform at present.

ELECTROCARDIOGRAM

(See also Chap. 247) Although an ECG usually should be recorded in patients with known or suspected heart disease, with the exception of the identification of arrhythmias, conduction abnormalities, ventricular hypertrophy, and acute myocardial infarction, it generally does not establish a specific diagnosis. The range of normal electrocardiographic findings is wide, and the tracing can be affected significantly by many noncardiac factors, such as age, body habitus, and serum electrolyte concentrations. In general, electrocardiographic changes should be interpreted in the context of other abnormal cardiovascular findings.

ASSESSMENT OF THE PATIENT WITH A HEART MURMUR

(Fig. 243-1) The cause of a heart murmur can often be readily elucidated from a systematic evaluation of its major attributes: timing, duration, intensity, quality, frequency, configuration, location, and radiation when considered in the light of the history, general physical examination, and other features of the cardiac examination, as described in Chap. 246.

The majority of heart murmurs are midsystolic and soft (grades I–II/VI). When such a murmur occurs in an asymptomatic child or young adult *without* other evidence of heart disease on clinical examination, it is usually benign and echocardiography generally is not required.

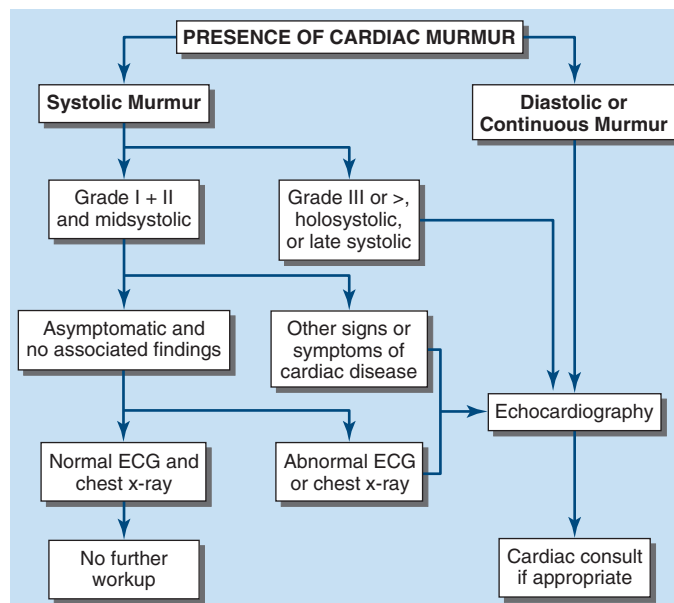


FIGURE 243-1 Approach to the evaluation of a heart murmur. ECG, electrocardiogram. (Reproduced with permission from E Braunwald, L Goldman [eds]: *Primary Cardiology*, 2nd ed. Philadelphia, Saunders, 2003.)

By contrast, two-dimensional and Doppler echocardiography (**Chap. 248**) are indicated in patients with loud systolic murmurs (grades $\geq$ III/VI), especially those that are holosystolic or late systolic, and in most patients with diastolic or continuous murmurs.

■ PITFALLS IN CARDIOVASCULAR MEDICINE

Increasing subspecialization in internal medicine and the perfection of advanced diagnostic techniques in cardiology can lead to several undesirable consequences. Examples include the following:

1. Failure by the *noncardiologist* to recognize important cardiac manifestations of systemic illnesses. For example, the presence of mitral stenosis, patent foramen ovale, and/or transient atrial arrhythmia should be considered in a patient with stroke, or the presence of pulmonary hypertension and cor pulmonale should be considered in a patient with scleroderma or Raynaud's syndrome. A cardiovascular examination should be carried out to identify and estimate the severity of the cardiovascular involvement that accompanies many noncardiac disorders.
2. Failure by the *cardiologist* to recognize underlying systemic disorders in patients with heart disease. For example, hyperthyroidism should be considered in an elderly patient with atrial fibrillation and unexplained heart failure, and Lyme disease should be considered in a patient with unexplained (fluctuating) atrioventricular block. A cardiovascular abnormality may provide the clue critical to the recognition of some systemic disorders. For example, an unexplained pericardial effusion may provide an early clue to the diagnosis of tuberculosis or a neoplasm.
3. Overreliance on and overutilization of laboratory tests, particularly invasive techniques, for the evaluation of the cardiovascular system. Cardiac catheterization and coronary arteriography (**Chap. 249**) provide precise diagnostic information that may be crucial in developing a therapeutic plan in patients with known or suspected CAD. Although a great deal of attention has been directed to these examinations, it is important to recognize that they serve to *supplement*, not *supplant*, a careful examination carried out with clinical and noninvasive techniques. A coronary arteriogram should not be performed in lieu of a careful history in patients with chest pain suspected of having ischemic heart disease. Although coronary arteriography may establish whether the coronary arteries are obstructed and to what extent, the results of the procedure by themselves often do not provide a definitive answer to the question of whether a patient's symptom of chest discomfort is attributable to coronary atherosclerosis and whether or not revascularization is indicated.

Despite the value of invasive tests in certain circumstances, they entail some small risk to the patient, involve discomfort and substantial cost, and place a strain on medical facilities. Therefore, they should be carried out only if the results can be expected to modify the patient's management.

■ DISEASE PREVENTION AND MANAGEMENT

The prevention of heart disease, especially of CAD, is one of the most important tasks of primary health care givers as well as cardiologists. Prevention begins with risk assessment, followed by attention to lifestyle, such as achieving optimal weight, physical activity, and smoking cessation, and then aggressive treatment of all abnormal risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus (**Chap. 415**).

After a complete diagnosis has been established in patients with known heart disease, a number of management options are usually available. Several examples may be used to demonstrate some of the principles of cardiovascular therapeutics:

1. In the absence of evidence of heart disease, the patient should be clearly informed of this assessment and *not* be asked to return at intervals for repeated examinations. If there is no evidence of disease, such continued attention may lead to the patient's developing inappropriate concern about the possibility of heart disease.
2. If there is no evidence of cardiovascular disease but the patient has one or more risk factors for the development of ischemic heart

disease (**Chap. 284**), a plan for their reduction should be developed and the patient should be retested at intervals to assess compliance and efficacy in risk reduction.

3. Asymptomatic or mildly symptomatic patients with valvular heart disease that is anatomically severe should be evaluated periodically, every 6–12 months, by clinical and noninvasive examinations. Early signs of deterioration of ventricular function may signify the need for surgical treatment before the development of disabling symptoms, irreversible myocardial damage, and excessive surgical risk (**Chap. 272**).
4. In patients with CAD (**Chap. 284**), available practice guidelines should be considered in the decision on the form of treatment (medical, percutaneous coronary intervention, or surgical revascularization). Mechanical revascularization may be employed too frequently in the United States and too infrequently in Eastern Europe and developing nations. The mere presence of angina pectoris and/or the demonstration of critical coronary arterial narrowing at angiography should not reflexively evoke a decision to treat the patient by revascularization. Instead, these interventions should be limited to patients with CAD in whom revascularization has been shown to improve the natural history (e.g., acute coronary syndrome or multivessel CAD with left ventricular dysfunction).

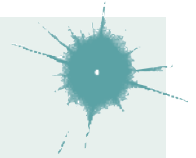
■ FURTHER READING

TSAO CW et al: Heart disease and stroke statistics—2023 update: A report from the American Heart Association. *Circulation* 147:e93, 2023.

244

Basic Biology of the Cardiovascular System

Joseph Loscalzo, John F. Keaney, Jr.,
Calum A. MacRae



DEVELOPMENTAL BIOLOGY OF THE CARDIOVASCULAR SYSTEM

The heart forms early during embryogenesis (**Fig. 244-1**), circulating blood, nutrients, molecular signals, and oxygen to the other developing organs while continuing to grow and undergo complex morphogenetic changes. Early cardiac progenitors arise within crescent-shaped fields of lateral splanchnic mesoderm under the influence of multiple cues and migrate to the midline to form the linear heart tube: a single layer of endocardium and a single layer of spontaneously beating cardiomyocytes.

The simple linear heart tube undergoes chamber specification and asymmetric looping, coordinated with longitudinal and concentric growth of different regions of the heart tube, to produce the presumptive atria and ventricles. Cells continue to migrate into the heart at both ends from additional heart fields in pharyngeal mesoderm as looping and growth occur. These cells exhibit distinctive gene expression (e.g., *Islet-1*) and distinctive physiology (e.g., calcium handling), contributing to discrete areas of the adult heart, including the right atrium and the right ventricle. These different embryonic origins of cells within the right and left ventricles correlate with distinctive single-cell RNA sequencing profiles decades later and help explain why some forms of congenital and adult cardiac diseases affect different regions of the heart.

After looping and chamber formation, a series of morphogenetic events divide the left side from the right side of the heart, separate the

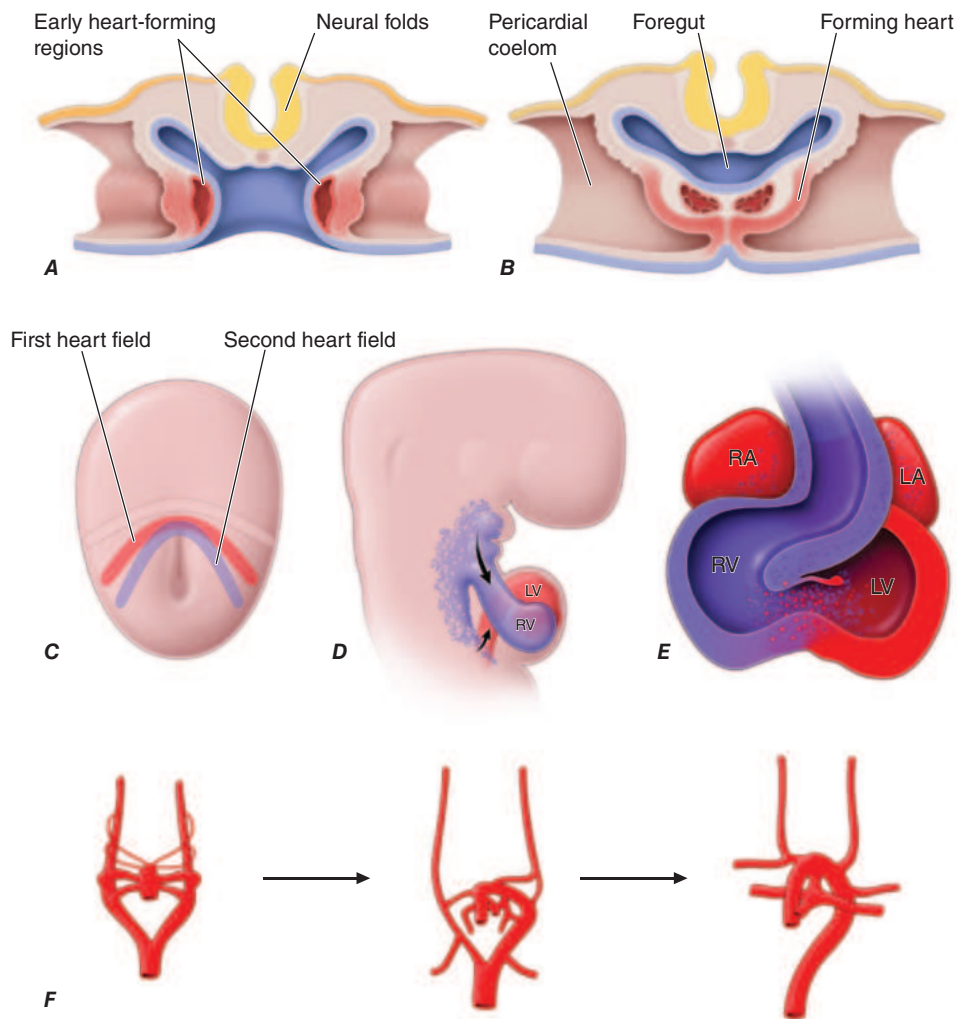


FIGURE 244-1 **A.** Schematic depiction of a transverse section through an early embryo depicts the bilateral regions where early heart tubes form. **B.** The bilateral heart tubes subsequently migrate to the midline and fuse to form the linear heart tube. **C.** At the early cardiac crescent stage of embryonic development, cardiac precursors include a primary heart field fated to form the linear heart tube and a second heart field fated to add myocardium to the inflow and outflow poles of the heart. **D.** Second heart field cells populate the pharyngeal region before subsequently migrating to the maturing heart. **E.** Large portions of the right ventricle and outflow tract and some cells within the atria derive from the second heart field. **F.** The aortic arch arteries form as symmetric sets of vessels that then remodel under the influence of the neural crest to form the asymmetric mature vasculature. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

atria from the ventricles, and fashion the aorta and pulmonary artery from the truncus arteriosus. Cardiac valves form between the atria and the ventricles and between the ventricles and the outflow vessels. Early in development, myocardial cells secrete an extracellular matrix rich in hyaluronic acid, or “cardiac jelly,” which accumulates within the endocardial cushions, precursors of the valves. Signals from overlying myocardial cells trigger migration, invasion, and phenotypic changes in underlying endocardial cells, an epithelial-mesenchymal transformation, that then invade and populate the endocardial cushion matrix. Mesenchymal cells then proliferate and form the mature valve leaflets.

The great vessels form as a series of symmetric bilateral aortic arch arteries that remodel asymmetrically to define the mature central vasculature. Migrating neural crest cells from the dorsal neural tube orchestrate this process and are necessary for aortic arch remodeling and septation of the truncus arteriosus. Smooth-muscle cells within the tunica media of the aortic arch, the ductus arteriosus, and the carotid arteries all derive from neural crest. By contrast, smooth muscle within the descending aorta arises from lateral plate mesoderm, and smooth muscle of the proximal outflow tract arises from the second heart field. Neural crest cells are sensitive to both vitamin A and folic acid, and congenital heart diseases involving abnormal remodeling of the aortic arch arteries are observed with maternal deficiencies of these vitamins. Shared embryonic origins of different cardiovascular cell types lead to

syndromic associations between various congenital heart diseases and a range of extracardiac abnormalities.

Coronary artery formation requires the addition of yet another cell population to the embryonic heart. Epicardial cells arise in the proepicardial organ, a derivative of the septum transversum, which also contributes to the fibrous portion of the diaphragm and to the liver. Proepicardial cells contribute smooth muscle to the coronary arteries and are required for proper coronary patterning. Other cell types within the heart (e.g., fibroblasts) also can arise from the proepicardium.

The cardiac conduction system, which generates and propagates electrical impulses, differentiates from cardiomyocyte precursors. The conduction system is composed of slow-conducting (proximal) components, such as the sinoatrial (SA) and atrioventricular (AV) nodes, as well as fast-conducting (distal) components, including the His bundle, bundle branches, and Purkinje fibers. Precursors within the sinus venosus give rise to the SA node, whereas those within the AV canal mature into heterogeneous cell types that compose the AV node. Decremental conduction through the AV node delays electrical impulses between atria and ventricles, enabling sequential antegrade contraction. The AV node also reduces the transmission of higher impulse rates to the vulnerable ventricle, whereas the distal conduction system rapidly propagates each impulse throughout the ventricles. The conduction system is composed of complex and heterogeneous cell populations with distinct gap junction proteins and ion channels that define the particular local electrical properties. Developmental defects in the conduction system can lead to clinical electrophysiologic

disorders, such as congenital heart block or pre-excitation (Wolff-Parkinson-White syndrome) ([Chap. 256](#)).

■ ORIGIN OF VASCULAR CELLS

Smooth-muscle cells are of varied origin. Some upper-body arterial smooth-muscle cells derive from the neural crest, whereas lower-body arteries develop smooth-muscle cells from neighboring mesodermal structures. Embryonic endothelial progenitor cells are derived from mesoderm. In adults, resident vascular or bone marrow-derived endothelial progenitors may aid repair of damaged or aging arteries. Bone marrow clonality, increasingly prevalent in aging, may impart significant clonality to endothelial cell populations. Vascular stem cells resident in the vessel wall may give rise to some smooth-muscle cells in injured or atheromatous arteries.

THE BLOOD VESSEL

■ VASCULAR ULTRASTRUCTURE

Blood vessels participate in disease biology as well as physiologic function in virtually every organ system. The smallest blood vessels—capillaries—consist of a monolayer of endothelial cells on a basement membrane adjacent to a discontinuous layer of smooth-muscle-like cells known as *pericytes* ([Fig. 244-2A](#)). Arteries typically have

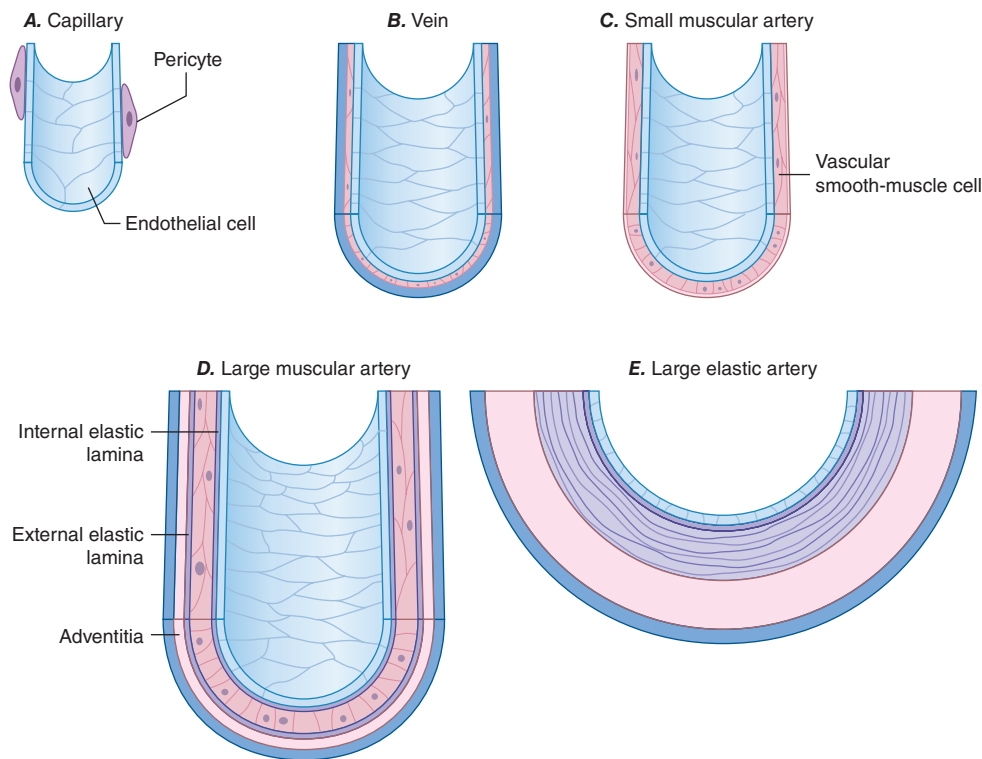


FIGURE 244-2 Schematics of the structures of various types of blood vessels. **A.** Capillaries consist of an endothelial tube in contact with a discontinuous population of pericytes. **B.** Veins typically have thin medias and thicker adventitias. **C.** A small muscular artery features a prominent tunica media. **D.** Larger muscular arteries have a prominent media with smooth-muscle cells embedded in a complex extracellular matrix. **E.** Larger elastic arteries have cylindrical layers of elastic tissue alternating with concentric rings of smooth-muscle cells as well as *vasa vasorum* to facilitate tissue blood supply.

a trilaminar structure (Fig. 244-2B–E). The *intima* consists of a monolayer of endothelial cells continuous with those of the capillaries. The middle layer, or *tunica media*, consists of a syncytium of smooth-muscle cells that in veins are much sparser than in arteries (Fig. 244-2B). The outer layer, or *adventitia*, consists of extracellular matrix with fibroblasts, mast cells, and nerve terminals. Larger arteries require nourishment of the tunica media that is accomplished via their own vasculature, the *vasa vasorum* (Fig. 244-2E).

Arterioles are small muscular arteries (Fig. 244-2C) that regulate blood pressure and flow through arterial beds. Medium-size muscular arteries also contain prominent smooth-muscle layers (Fig. 244-2D) that participate in atherogenesis. Larger elastic arteries have a highly structured tunica media with concentric bands of smooth-muscle cells, interspersed with strata of elastin-rich extracellular matrix (Fig. 244-2E). Larger arteries form an internal elastic lamina between intima and media while an external elastic lamina partitions the media from surrounding adventitia.

VASCULAR CELL BIOLOGY

Endothelial Cell The endothelium forms the interface between tissues and the blood compartment, regulating the passage of molecules and cells. This function of endothelial cells as a selectively permeable barrier fails in vascular diseases, including atherosclerosis, hypertension, and renal disease, as well as in pulmonary edema, sepsis, and other situations exhibiting “capillary leak.”

The endothelium also participates in the local regulation of vascular tone and blood flow. Endogenous endothelium-derived substances, such as prostacyclin, endothelium-derived hyperpolarizing factor, nitric oxide (NO), and hydrogen peroxide (H₂O₂), provide tonic stimulation of endothelial homeostatic properties under physiologic conditions in vivo (Table 244-1). Impaired production or excess catabolism of these substances can mediate dysfunctional properties of the endothelium. A major homeostatic influence on the endothelium is laminar blood flow, and the measurement of flow-mediated dilatation directly assesses endothelial vasodilator function in humans (Fig. 244-3).

Endothelial cells also produce potent vasoconstrictor substances such as endothelin. Excessive production of reactive oxygen species, such as superoxide anion (O₂^{•−}), by endothelial or smooth-muscle cells under pathologic conditions (e.g., excessive exposure to angiotensin II) can promote local oxidative stress and inactivate NO.

Endothelial cells also regulate cellular traffic through tissues. Normal endothelium exhibits limited interaction with circulating leukocytes, but bacterial products such as endotoxin or proinflammatory cytokines can induce endothelial cells to express an array of adhesion molecules that selectively bind various classes of leukocytes in different pathologic conditions. The adhesion molecules and chemokines generated during acute bacterial infection tend to recruit granulocytes, while in chronic inflammatory diseases such as tuberculosis or atherosclerosis, the adhesion molecules expressed favor monocyte recruitment. Endothelial cell injury participates in the pathophysiology of many immune-mediated diseases. For example, complement-mediated lysis of endothelial cells contributes to tissue injury. The foreign histocompatibility complex antigens on endothelial cells in solid-organ allografts can promote allograft arteriopathy, while immune-mediated endothelial injury also plays a role in thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome.

The endothelium also regulates the balance between thrombosis and hemostasis through a highly tuned set of regulatory pathways. For example, inflammatory cytokines, bacterial endotoxin, or angiotensin II can activate endothelial cells to produce substantial quantities of plasminogen activator inhibitor 1 (PAI-1), the major inhibitor of fibrinolysis. Inflammatory stimuli also induce endothelial expression of the potent procoagulant tissue factor, a contributor to disseminated intravascular coagulation in sepsis; similar effects are observed in hyperglycemia. Thus, in pathologic circumstances, endothelial dysfunction tends to promote local thrombus accumulation rather than combat it.

Endothelial cells regulate the growth of subjacent smooth-muscle cells by elaborating heparan sulfate glycosaminoglycans that inhibit smooth-muscle proliferation. In the setting of vascular injury, endothelium-derived growth factors and chemoattractants (e.g., platelet-derived growth factor) induce the migration and proliferation of vascular smooth-muscle cells. Dysregulation of these growth-stimulatory molecules may promote smooth-muscle accumulation in atherosclerotic lesions.

TABLE 244-1 Endothelial Functions in Health and Disease

HOMEOSTATIC PROPERTIES	DYSFUNCTIONAL PROPERTIES
Optimize balance between vasodilation and vasoconstriction	Impaired dilation, vasoconstriction
Antithrombotic, profibrinolytic	Prothrombotic, antifibrinolytic
Anti-inflammatory	Proinflammatory
Antiproliferative	Proproliferative
Antioxidant	Prooxidant
Selective permeability	Impaired barrier function

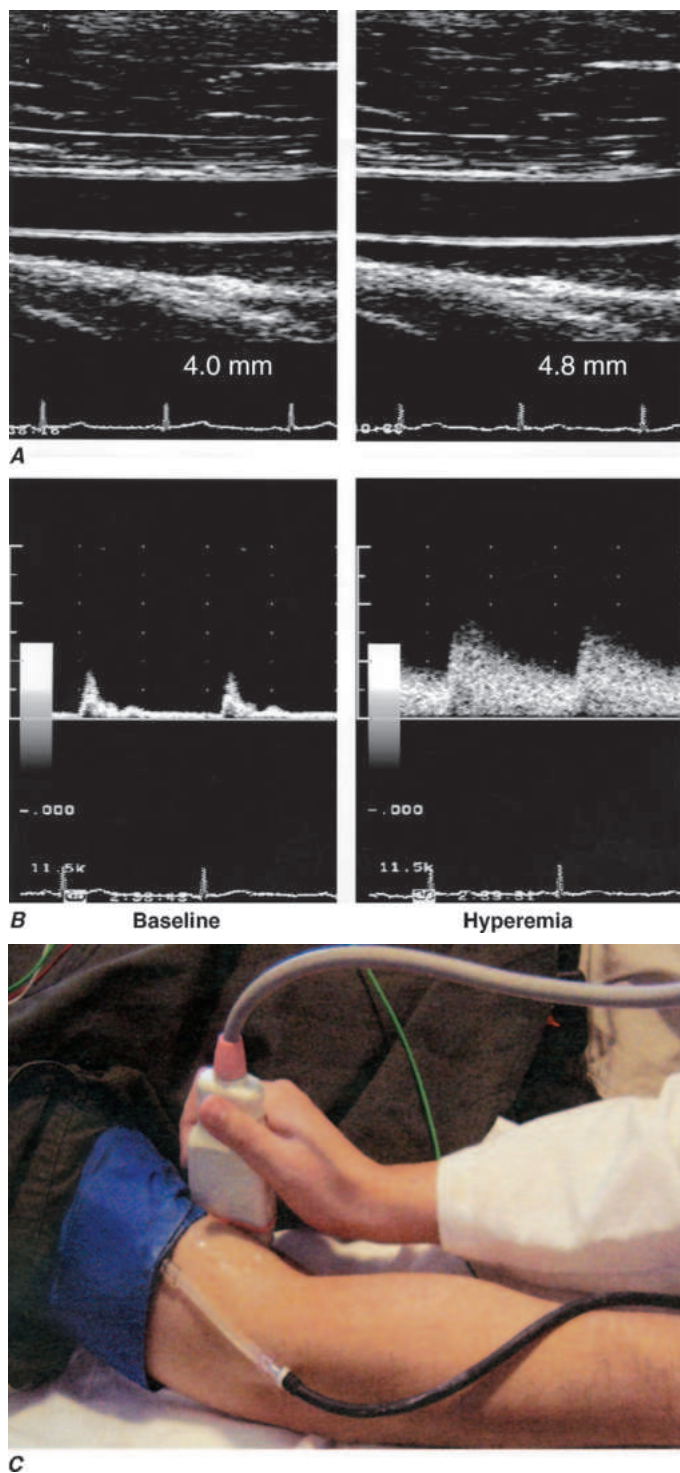


FIGURE 244-3 Assessment of endothelial function in vivo using blood pressure cuff occlusion and release. Upon deflation of the cuff, an ultrasound probe monitors changes in diameter (**A**) and blood flow (**B**) of the brachial artery (**C**). (Reproduced with permission of J. Vita, MD.)

Vascular Smooth-Muscle Cell Contraction and relaxation of vascular smooth-muscle cells in muscular arteries determine blood pressure, regional flow, and the afterload experienced by the left ventricle (see below). Venous tone regulates venous tree capacitance and influences ventricular preload. Smooth-muscle cells in the adult vessel seldom replicate in the absence of arterial injury or inflammatory activation, but proliferation and migration of arterial smooth-muscle cells contribute to arterial stenoses in atherosclerosis, arteriolar remodeling in hypertension, and the hyperplastic response of arteries to injury. In the pulmonary circulation, smooth-muscle migration and proliferation underlie the vascular pathology that occurs in sustained high-flow

states such as left-to-right shunts in congenital heart disease with resulting pulmonary hypertension.

Smooth-muscle cells secrete the bulk of vascular extracellular matrix. Excessive production of collagen and glycosaminoglycans contributes to the remodeling, altered biomechanics, and physiology of arteries affected by hypertension or atherosclerosis. In larger elastic arteries, such as the aorta, the ability to store the kinetic energy of systole promotes tissue perfusion during diastole. Arterial stiffness, associated with aging or disease, increases left ventricular afterload and portends a poor outcome.

Like endothelial cells, vascular smooth-muscle cells not only respond to paracrine stimuli from other cells but can themselves serve as a source of such stimuli. For example, proinflammatory stimuli induce smooth-muscle cells to elaborate cytokines and other mediators that drive thrombosis and fibrinolysis as well as proliferation.

Vascular Smooth-Muscle Cell Contraction The principal mechanism for vascular smooth-muscle cell contraction is increased cytoplasmic calcium concentration due to transmembrane influx and triggered release from intracellular calcium stores (Fig. 244-4). In vascular smooth-muscle cells, voltage-dependent L-type calcium channels open with membrane depolarization. Local influx of calcium, termed *calcium sparks*, can trigger release from intracellular stores, which results in more contraction and increased vessel tone (see below). Opposing currents balance the effects of individual ionic fluxes promoting homeostasis, which is tightly regulated by neural and metabolic influences.

Vasoconstricting agonists also increase intracellular $[Ca^{2+}]$ by various mechanisms including receptor-dependent phospholipase C activation producing hydrolysis of phosphatidylinositol 4,5-bisphosphate to generate diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). These membrane lipid derivatives, in turn, activate protein kinase C and increase intracellular $[Ca^{2+}]$. In addition, IP_3 binds specific sarcoplasmic reticulum (SR) receptors to increase calcium efflux from this storage pool into the cytoplasm.

Vascular smooth-muscle cell contraction depends on myosin light chain phosphorylation that reflects the balance between the activity of relevant kinases and phosphatases. Calcium activates myosin light chain kinase via calmodulin, augmenting myosin ATPase activity and enhancing contraction. Conversely, myosin light chain phosphatase reduces myosin ATPase activity and contractile force. Other kinase/phosphorylase combinations result in a complex regulatory network that refines vascular tone and links it to physiologic requirements.

Control of Vascular Smooth-Muscle Cell Tone The autonomic nervous system and endothelial cells modulate vascular smooth-muscle cells through similar convergent pathways. Autonomic neurons enter vessel media and modulate vascular smooth-muscle cell tone in response to baroreceptors and chemoreceptors within the aortic arch or carotid bodies and to thermoreceptors in the skin. Rapidly acting reflex arcs modulated by central inputs respond to multiple sensory inputs as well as emotional stimuli through three neuronal classes: *sympathetic*, whose principal neurotransmitters are epinephrine and norepinephrine; *parasympathetic*, whose principal neurotransmitter is acetylcholine; and *nonadrenergic/noncholinergic*, which include two subgroups—*nitrergic*, whose principal neurotransmitter is NO, and *peptidergic*, whose principal neurotransmitters are substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and the nonpeptide, adenosine triphosphate (ATP).

Each of these neurotransmitters acts through specific receptors on the vascular smooth-muscle cell to modulate intracellular Ca^{2+} and, consequently, contractile tone. Norepinephrine activates α -adrenergic receptors, and epinephrine activates both α and β receptors. In most blood vessels, norepinephrine activates postjunctional α_1 receptors in large arteries and α_2 receptors in small arteries and arterioles, leading to vasoconstriction. Most blood vessels express β_2 -adrenergic receptors on their vascular smooth-muscle cells and respond to β agonists by cyclic AMP-dependent relaxation. Acetylcholine released from parasympathetic neurons may bind to muscarinic receptors on either vascular smooth-muscle cells, causing vasoconstriction, or on

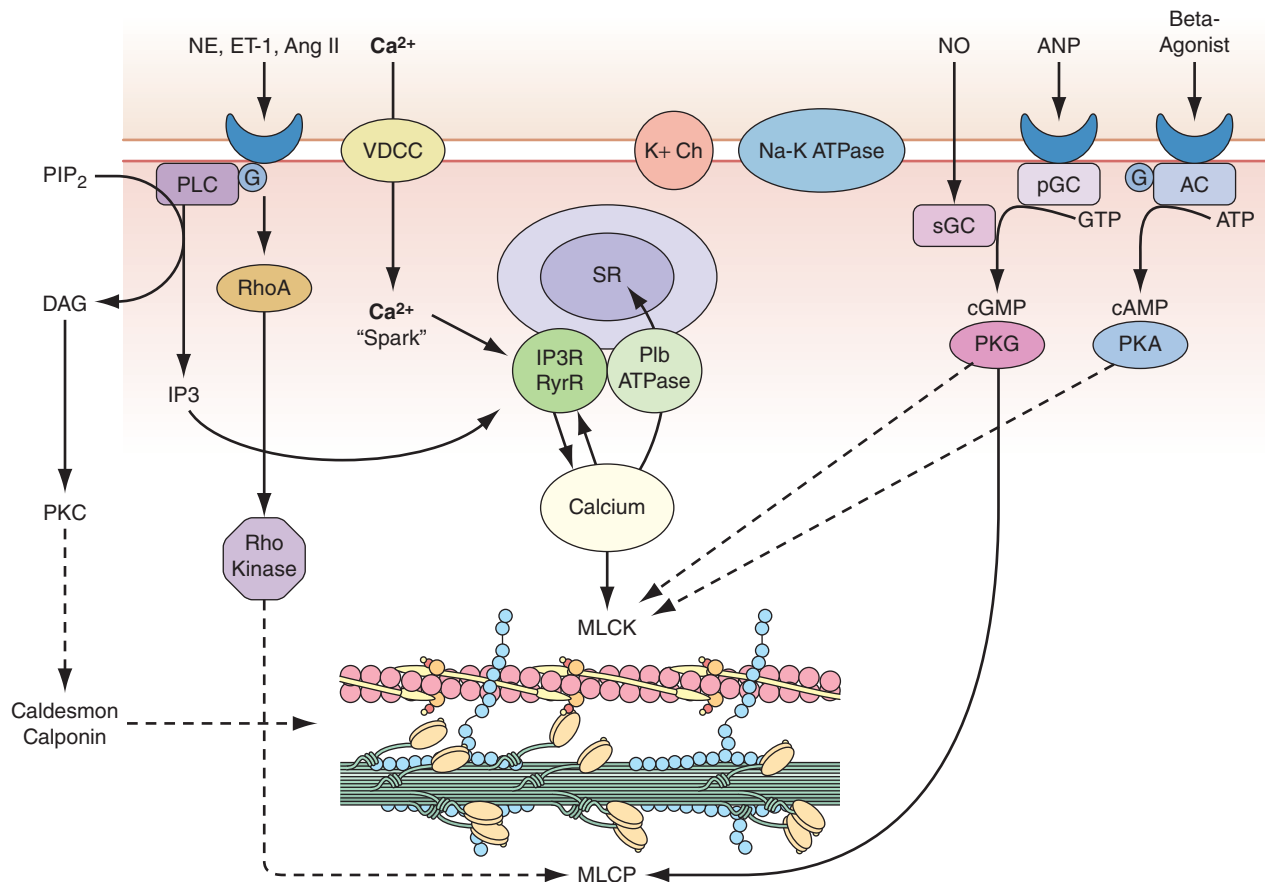


FIGURE 244-4 Regulation of vascular smooth-muscle cell calcium concentration and actomyosin ATPase-dependent contraction. AC, adenylyl cyclase; Ang II, angiotensin II; ANP, atrial natriuretic peptide; DAG, diacylglycerol; ET-1, endothelin-1; G, G protein; IP₃, inositol 1,4,5-trisphosphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NE, norepinephrine; NO, nitric oxide; pGC, particulate guanylyl cyclase; PIP₂, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; sGC, soluble guanylyl cyclase; SR, sarcoplasmic reticulum; VDCC, voltage-dependent calcium channel. *Solid lines depict stimulatory interaction, and dashed lines represent inhibition.* (Reproduced with permission from B Berk, in *Vascular Medicine*, 3rd ed. Philadelphia, Saunders, Elsevier; 2006.)

endothelial cells, causing NO-dependent vasorelaxation. Nitroergic neurons release NO, which relaxes vascular smooth-muscle cell via the cyclic GMP-dependent and -independent mechanisms outlined, and other peptidergic inputs that regulate vascular tone. **For the detailed molecular physiology of the autonomic nervous system, see Chap. 451.**

The release of endothelial effectors of vascular smooth-muscle cell tone integrates the smooth-muscle response to mechanical (e.g., shear stress, cyclic strain) and biochemical stimuli (purinergic agonists, muscarinic agonists, peptidergic agonists). In addition to these local paracrine modulators, a complex system of circulating modulators ranging from norepinephrine to the natriuretic peptides also modify vascular smooth-muscle cell tone.

■ ARTERIOGENESIS AND ANGIOGENESIS

Recruitment and growth of blood vessels (arteriogenesis) and new capillaries (angiogenesis) can occur in response to conditions such as chronic hypoxemia and tissue ischemia. Growth factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), can activate a signaling cascade that stimulates endothelial proliferation and tube formation, defined as *angiogenesis*. Guidance molecules, including members of the semaphorin family of secreted peptides, direct blood vessel patterning by attracting or repelling nascent endothelial tubes. The recruitment and expansion of preexisting collateral vascular networks in response to a blocked artery, an example of arteriogenesis, can result from selective activation of both growth factors and, perhaps, local or circulating endothelial progenitor cells. True vascular regeneration, or the development of a new blood vessel that includes all three cell layers, normally does not occur in adult mammals, but recent scientific advances might help obviate such limitations.

CELLULAR BASIS OF CARDIAC CONTRACTION

■ CARDIAC ULTRASTRUCTURE

Most of the ventricular mass is composed of cardiomyocytes, normally 60–140 μm in length and 17–25 μm in diameter (**Fig. 244-5A**). Each cell contains multiple myofibrils that run the length of the cell and are composed of series of repeating sarcomeres. The cytoplasm between the myofibrils contains other cell constituents, including a single centrally located nucleus, mitochondria, and the intracellular membrane system, the SR.

The *sarcomere*, the structural and functional unit of contraction, lies between adjacent Z lines, which on transmission electron microscopy are seen as dark repeating bands. The distance between Z lines varies with the degree of contraction or stretch of the muscle and ranges between 1.6 and 2.2 μm . At the center of the sarcomere is a dark band of constant length (1.5 μm), the A band, which is flanked by two lighter bands, the I bands, which are of variable length. The sarcomere of heart muscle, like that of skeletal muscle, consists of interdigitating thick and thin myofilaments. Thicker filaments, composed principally of the protein myosin, traverse the A band; they are about 10 nm (100 $\text{\AA}$) in diameter, with tapered ends. Thinner filaments, composed primarily of actin, course from the Z lines through the I band into the A band; they are ~5 nm (50 $\text{\AA}$) in diameter and 1.0 μm in length. Thus, thick and thin filaments overlap only within the (dark) A band, whereas the (light) I band contains only thin filaments. On electron-microscopic examination, bridges extend between the thick and thin filaments within the A band; these are myosin heads (see below) bound to actin filaments.

■ THE CONTRACTILE PROCESS

The sliding filament model for muscle contraction rests on the central observation that both the thick and the thin filaments are constant in

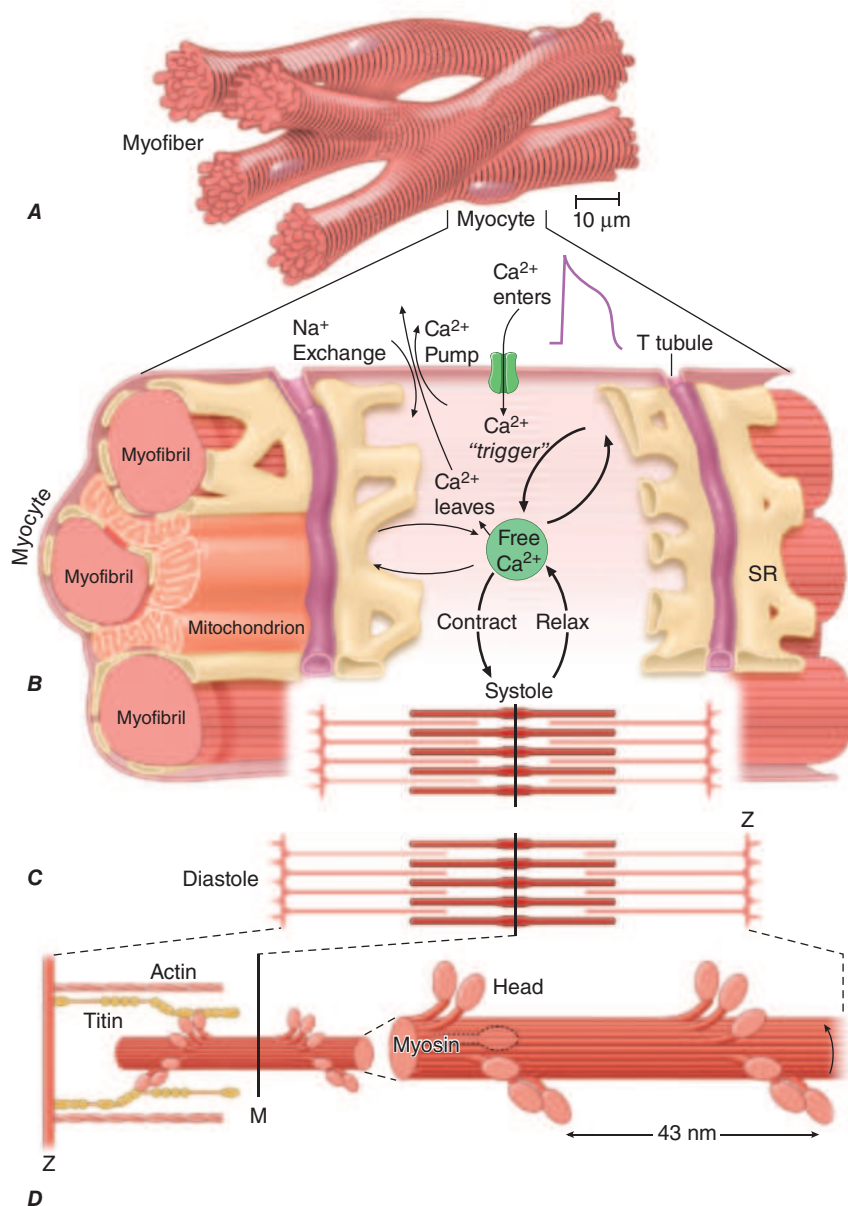


FIGURE 244-5 **A** shows the branching myocytes making up the cardiac myofibers. **B** illustrates the critical role played by the changing $[Ca^{2+}]$ in the myocardial cytosol. Ca^{2+} ions are schematically shown as entering through the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma. These Ca^{2+} ions "trigger" the release of more calcium from the sarcoplasmic reticulum (SR) and thereby initiate a contraction-relaxation cycle. Eventually the small quantity of Ca^{2+} that has entered the cell leaves predominantly through an Na^+/Ca^{2+} exchanger, with a lesser role for the sarcolemmal Ca^{2+} pump. The varying actin-myosin overlap is shown for **(B)** systole, when $[Ca^{2+}]$ is maximal, and **(C)** diastole, when $[Ca^{2+}]$ is minimal. **D**. The myosin heads, attached to the thick filaments, interact with the thin actin filaments. (Reproduced with permission from LH Opie: *Heart Physiology: From Cell to Circulation*, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004.)

length during both contraction and relaxation. With activation, the actin filaments are propelled farther into the A band. In this process, the A band remains constant in length, whereas the I band shortens and the Z lines move toward one another.

The *myosin* molecule is a complex, asymmetric protein with a molecular mass of about 500,000 Da; it has a rod-like portion that is about 150 nm (1500 Å) in length with a globular portion (head) at its end. The globular portions of myosin form the bridges to actin and are the site of ATPase activity. In thick myofilaments, composed of ~300 longitudinally stacked myosin molecules, the rod-like segments of myosin assume an orderly, polarized orientation, with outwardly projecting globular heads interacting with actin to generate force and shorten (Fig. 244-5B).

Actin has a molecular mass of about 47,000 Da. Thin filaments consist of a double helix of two chains of actin molecules wound about each other on a larger molecule, tropomyosin. A group of regulatory proteins—troponins C, I, and T—localize at regular intervals on this filament (Fig. 244-6). In contrast to myosin, actin lacks intrinsic enzymatic activity but combines reversibly with myosin in the presence of

ATP and Ca^{2+} . Calcium activates the myosin ATPase, which breaks down ATP to supply the energy for contraction (Fig. 244-6). The activity of myosin ATPase determines the rate of actomyosin cross-bridge formation and breakdown, and ultimately determines contraction velocity. In relaxed muscle, tropomyosin inhibits this interaction. *Titin* (Fig. 244-5D) an enormous, flexible, myofibrillar protein, connects myosin to the Z line; its elasticity contributes to the passive mechanical characteristics of the heart. Dystrophin, a cytoskeletal protein that binds to the dystroglycan complex at membrane adherens junctions, tethers the sarcomere to the cell membrane at these regions of tight coupling to adjacent myocytes. Mutations in multiple sarcomeric and cytoskeletal proteins cause different Mendelian disorders involving the heart and skeletal muscle and also sensitize individuals to toxic cardiomyopathies (e.g., due to alcohol or chemotherapy) and to those caused by other acquired stressors, such as inflammatory or peripartum cardiomyopathy.

During activation of the cardiac myocyte, Ca^{2+} binds the heterotrimer troponin C, resulting in regulatory conformational changes in tropomyosin and exposing actin cross-bridge interaction sites

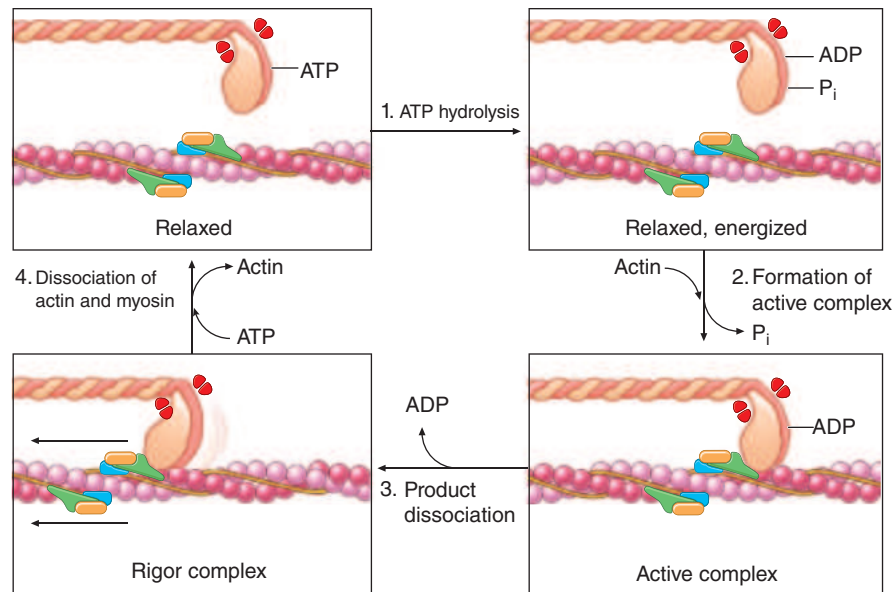


FIGURE 244-6 Four steps in cardiac muscle contraction and relaxation. In relaxed muscle (*upper left*), ATP bound to the myosin cross-bridge dissociates the thick and thin filaments. **Step 1:** Hydrolysis of myosin-bound ATP by the ATPase site on the myosin head transfers the chemical energy of the nucleotide to the activated cross-bridge (*upper right*). When cytosolic Ca^{2+} concentration is low, as in relaxed muscle, the reaction cannot proceed because tropomyosin and the troponin complex on the thin filament do not allow the active sites on actin to interact with the cross-bridges. Therefore, even though the cross-bridges are energized, they cannot interact with actin. **Step 2:** When Ca^{2+} binding to troponin C has exposed active sites on the thin filament, actin interacts with the myosin cross-bridges to form an active complex (*lower right*) in which the energy derived from ATP is retained in the actin-bound cross-bridge, whose orientation has not yet shifted. **Step 3:** The muscle contracts when ADP dissociates from the cross-bridge. This step leads to the formation of the low-energy rigor complex (*lower left*) in which the chemical energy derived from ATP hydrolysis has been expended to perform mechanical work (the “rowing” motion of the cross-bridge). **Step 4:** The muscle returns to its resting state, and the cycle ends when a new molecule of ATP binds to the rigor complex and dissociates the cross-bridge from the thin filament. This cycle continues until calcium is dissociated from troponin C in the thin filament, which causes the contractile proteins to return to the resting state with the cross-bridge in the energized state. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase. (Reproduced with permission from AM Katz: *Heart failure: Cardiac function and dysfunction*, in *Atlas of Heart Diseases*, 3rd ed, WS Colucci [ed]. Philadelphia, Current Medicine, 2002.)

(Fig. 244-6). Repetitive interaction between myosin heads and actin filaments is termed *cross-bridge cycling* and results in sliding of the actin along the myosin filaments, with muscle shortening and/or the development of tension. The splitting of ATP then dissociates the myosin cross-bridge from actin. In the presence of ATP (Fig. 244-6), actin and myosin filaments bind and dissociate cyclically if sufficient Ca^{2+} is present; these processes cease when $[\text{Ca}^{2+}]$ falls below a critical level, and the troponin-tropomyosin complex once more inhibits actin-myosin interactions (Fig. 244-7).

Cytoplasmic $[\text{Ca}^{2+}]$ is a principal determinant of the inotropic state of the heart. Most agents that stimulate myocardial contractility (positive inotropic stimuli), including digitalis glycosides and β -adrenergic agonists, increase cytoplasmic $[\text{Ca}^{2+}]$, triggering cross-bridge cycling. Increased adrenergic neuronal activity stimulates myocardial contractility through norepinephrine release, activation of β -adrenergic receptors, and, via G_s -stimulated guanine nucleotide-binding proteins, activation of the adenyl cyclase, which leads to the formation of the intracellular second messenger cyclic AMP from ATP (Fig. 244-7). Cyclic AMP in turn activates protein kinase A (PKA), which phosphorylates sarcolemmal Ca^{2+} channels, thereby enhancing the influx of Ca^{2+} into the myocyte.

The SR (Fig. 244-8), a complex network of anastomosing intracellular channels, invests the myofibrils. The transverse tubules, or T system, closely related to the SR, both structurally and functionally, arise as sarcolemmal invaginations that extend into the myofibrillar bundles along the Z lines, i.e., the ends of the sarcomeres.

■ CARDIAC ACTIVATION

In the inactive state, the cardiomyocyte membrane is electrically polarized; i.e., the interior has a negative charge relative to the outside of the cell, with a transmembrane potential of -80 to -100 mV (Chap. 250). The sarcolemma, which in the resting state is largely impermeable to Na^+ , and a Na^+ - and K^+ -pump energized by ATP extrudes Na^+ from the cell and maintains the resting potential. In this resting state, intracellular $[\text{K}^+]$ is relatively high and $[\text{Na}^+]$ is far lower;

conversely, extracellular $[\text{Na}^+]$ is high and $[\text{K}^+]$ is low. At the same time, extracellular $[\text{Ca}^{2+}]$ greatly exceeds free intracellular $[\text{Ca}^{2+}]$.

The action potential has four phases (see Fig. 250-1B). Depolarizing current spreads across the cell membrane, penetrating deeply into the cell via the T tubular system. During the action potential plateau (phase 2), there is a slow inward current through sarcolemmal L-type Ca^{2+} channels (Fig. 244-8). The absolute quantity of Ca^{2+} traversing sarcolemmal and T tubular membranes is modest and insufficient to fully activate contraction. However, this initial Ca^{2+} current, through Ca^{2+} -induced Ca^{2+} release, triggers substantial Ca^{2+} release from the SR, inducing contraction.

Ca^{2+} is released from the SR through a Ca^{2+} release channel, a cardiac isoform of the ryanodine receptor (RyR2). Several regulatory proteins inhibit RyR2 and thus SR Ca^{2+} release. Inherited disorders or exogenous factors affecting the efficiency or stability of SR Ca^{2+} handling can impair contraction, leading to heart failure or to ventricular arrhythmias.

The Ca^{2+} released from the SR diffuses to interact with myofibrillar troponin C (Fig. 244-7), repressing this protein's inhibition of contraction, and so activating myofilaments to shorten. During repolarization, the activity of the SR Ca^{2+} -ATPase (SERCA_{2A}) leads to Ca^{2+} uptake against a concentration gradient into the SR where it complexes with another specialized protein, *calsequestrin*. The uptake of Ca^{2+} is ATP (energy)-dependent and lowers cytoplasmic $[\text{Ca}^{2+}]$ to a level where actomyosin interaction is inhibited and myocardial relaxation occurs. There is also a sarcolemmal exchange of Ca^{2+} for Na^+ (Fig. 244-8), reducing cytoplasmic $[\text{Ca}^{2+}]$. Additional control of calcium compartmentalization results from cyclic AMP-dependent PKA phosphorylation of the SR protein *phospholamban*, permitting SERCA_{2A} activation, increasing SR Ca^{2+} uptake, and so accelerating relaxation rates, and loading the SR with Ca^{2+} for subsequent cycles of release and contraction.

Thus, the combination of the cell membrane, transverse tubules, and SR, transmitting the action potential, releasing and then re-accumulating Ca^{2+} , controls the cyclic contraction and relaxation of heart muscle.

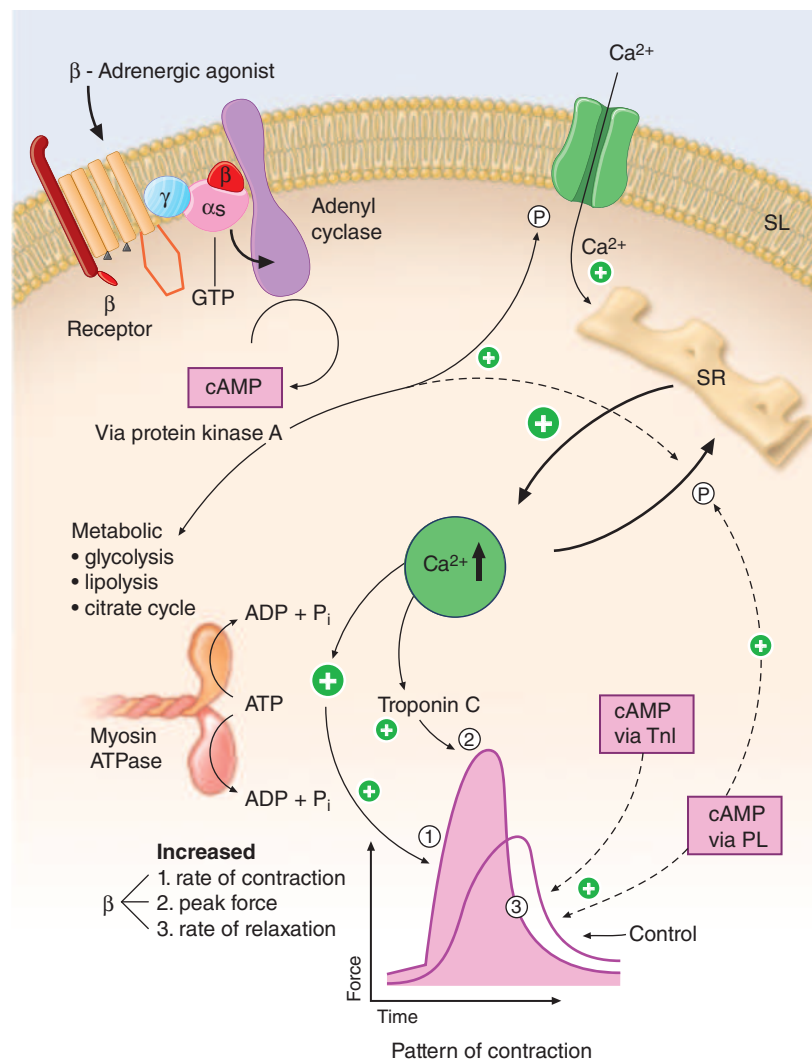


FIGURE 244-7 Signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects of α -adrenergic stimulation. When the β -adrenergic agonist interacts with the β receptor, a series of G protein-mediated changes leads to activation of adenylyl cyclase and the formation of cyclic adenosine monophosphate (cAMP). The latter acts via protein kinase A to stimulate metabolism (left) and phosphorylate the Ca^{2+} channel protein (right). The result is an enhanced opening probability of the Ca^{2+} channel, thereby increasing the inward movement of Ca^{2+} ions through the sarcolemma (SL) of the T tubule. These Ca^{2+} ions release more calcium from the sarcoplasmic reticulum (SR) to increase cytosolic Ca^{2+} and activate troponin C. Ca^{2+} ions also increase the rate of breakdown of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (P_i). Enhanced myosin ATPase activity explains the increased rate of contraction, with increased activation of troponin C explaining increased peak force development. An increased rate of relaxation results from the ability of cAMP to activate as well the protein phospholamban, situated on the membrane of the SR, that controls the rate of uptake of calcium into the SR. The latter effect explains enhanced relaxation (lusitropic effect). P, phosphorylation; PL, phospholamban; TnI, troponin I. (Reproduced with permission from LH Opie: *Heart Physiology: From Cell to Circulation*, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004.)

Genetic or pharmacologic alterations of any component can disturb any of the functions of this finely tuned system.

CONTROL OF CARDIAC PERFORMANCE AND OUTPUT

The extent of shortening of heart muscle and, therefore, ventricular stroke volume in the intact heart depends on three major influences: (1) the length of the muscle at the onset of contraction, i.e., the preload; (2) the tension that the muscle must develop during contraction, i.e., the afterload; and (3) muscle contractility, i.e., the extent and velocity of shortening at any given preload and afterload. Table 244-2 lists the major determinants of preload, afterload, and contractility.

THE ROLE OF MUSCLE LENGTH (PRELOAD)

Preload determines sarcomere length at the onset of contraction. Contractile force is optimal at specific sarcomere lengths ($\sim 2.2 \mu\text{m}$) where both myofilament Ca^{2+} sensitivity is maximal, and myofilament interactions and activation of contraction are most efficient. The relationship between initial muscle fiber length and the developed force is the basis of Starling's law of the heart, which states that, within limits,

the ventricular contraction force depends on the end-diastolic length of the cardiac muscle; in vivo, end-diastolic length relates closely to the ventricular end-diastolic volume.

CARDIAC PERFORMANCE

Ventricular end-diastolic or "filling" pressure can serve as a surrogate for end-diastolic volume. In isolated heart and heart-lung preparations, stroke volume varies directly with the end-diastolic fiber length (preload) and inversely with the arterial resistance (afterload), and as the heart fails—i.e., as its contractility declines—it delivers a progressively smaller stroke volume from a normal or even elevated end-diastolic volume. The relation between ventricular end-diastolic pressure and the stroke work of the ventricle (the ventricular function curve) provides a working definition of cardiac contractility in the intact organism. An increase in contractility is accompanied by a shift of the ventricular function curve upward and to the left (greater stroke work at any level of ventricular end-diastolic pressure, or lower end-diastolic volume at any level of stroke work), whereas a shift downward and to the right characterizes reduction of contractility (Fig. 244-9).

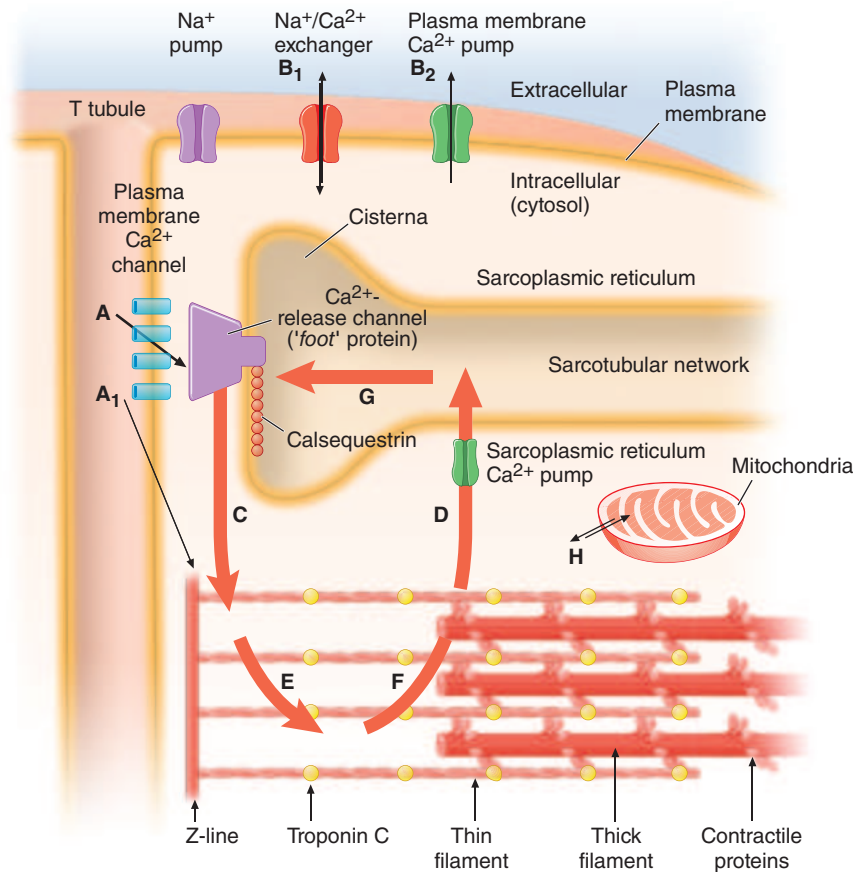


FIGURE 244-8 The Ca^{2+} fluxes and key structures involved in cardiac excitation-contraction coupling. The arrows denote the direction of Ca^{2+} fluxes. The thickness of each arrow indicates the magnitude of the calcium flux. Two Ca^{2+} cycles regulate excitation-contraction coupling and relaxation. The larger cycle is entirely intracellular and involves Ca^{2+} fluxes into and out of the sarcoplasmic reticulum, as well as Ca^{2+} binding to and release from troponin C. The smaller extracellular Ca^{2+} cycle occurs when this cation moves into and out of the cell. The action potential opens plasma membrane Ca^{2+} channels to allow passive entry of Ca^{2+} into the cell from the extracellular fluid (arrow A). Only a small portion of the Ca^{2+} that enters the cell directly activates the contractile proteins (arrow A₁). The extracellular cycle is completed when Ca^{2+} is actively transported back out to the extracellular fluid by way of two plasma membrane fluxes mediated by the sodium-calcium exchanger (arrow B₁) and the plasma membrane calcium pump (arrow B₂). In the intracellular Ca^{2+} cycle, passive Ca^{2+} release occurs through channels in the cisternae (arrow C) and initiates contraction; active Ca^{2+} uptake by the Ca^{2+} pump of the sarcotubular network (arrow D) relaxes the heart. Diffusion of Ca^{2+} within the sarcoplasmic reticulum (arrow G) returns this activator cation to the cisternae, where it is stored in a complex with calsequestrin and other calcium-binding proteins. Ca^{2+} released from the sarcoplasmic reticulum initiates systole when it binds to troponin C (arrow E). Lowering of cytosolic $[\text{Ca}^{2+}]$ by the sarcoplasmic reticulum (SR) causes this ion to dissociate from troponin (arrow F) and relaxes the heart. Ca^{2+} also may move between mitochondria and cytoplasm (H). (Reproduced with permission from AM Katz: *Physiology of the Heart*, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2005.)

■ VENTRICULAR AFTERLOAD

In the intact heart, as *ex vivo*, the extent and velocity of shortening of ventricular muscle fibers at any level of preload and of myocardial contractility relate inversely to the afterload, i.e., the instantaneous load opposing shortening. In the intact heart, the afterload may be defined as the tension developed in the ventricular wall during ejection. Afterload is determined by the aortic pressure as well as by the volume of the ventricular cavity and myocardial tissue characteristics including thickness. Laplace's law models the tension of the myocardial fiber as the product of intra-cavitary ventricular pressure and ventricular radius divided by wall thickness. Therefore, at any given aortic pressure, the afterload on a dilated left ventricle exceeds that on a normal-sized ventricle. Conversely, at the same aortic pressure and ventricular diastolic volume, the afterload on a hypertrophied ventricle is lower than that on a normal chamber. Aortic pressure in turn depends on the peripheral vascular resistance, the biomechanics of the arterial tree, and the volume of blood it contains at the onset of ejection.

Ventricular afterload finely regulates cardiovascular performance (Fig. 244-10). As noted, elevations in both preload and contractility increase myocardial fiber shortening, whereas increases in afterload reduce it. The extent of myocardial fiber shortening and left ventricular size determine stroke volume. An increase in arterial pressure induced by vasoconstriction, for example, augments afterload, which opposes myocardial fiber shortening, reducing stroke volume.

When myocardial contractility is impaired and the ventricle dilates, afterload rises (Laplace's law) and limits cardiac output. Increased afterload also may result from neural and humoral stimuli that occur in response to a fall in cardiac output. This increased afterload may reduce cardiac output further, thereby increasing ventricular volume and initiating a vicious circle, especially in patients with ischemic heart disease and limited myocardial O_2 supply. Treatment with vasodilators has the opposite effect; when afterload falls, cardiac output rises (Chaps. 266–270).

Under normal circumstances, the various influences acting on cardiac performance interact in a complex fashion to maintain cardiac output at a level responsive to the requirements of tissue metabolic demands (Fig. 244-10). Interference with a single mechanism may not influence the cardiac output due to homeostatic adjustments. For example, a moderate reduction of blood volume or the loss of the atrial contribution to ventricular contraction can be tolerated without a reduction in resting cardiac output. Under these circumstances, other factors, such as adrenergic neuronal impulses increasing cardiac contractility, heart rate, and venous tone, will serve as compensatory mechanisms and sustain cardiac output in a normal individual. Ultimately, understanding the complex interactions between so many different phasic variables requires rigorous models to predict relevant outcomes, and led to the early application of systems engineering principles in medicine.

TABLE 244-2 Determinants of Stroke Volume

I. Ventricular Preload

- A. Blood volume
- B. Distribution of blood volume
 - 1. Body position
 - 2. Intrathoracic pressure
 - 3. Intrapericardial pressure
 - 4. Venous tone
 - 5. Pumping action of skeletal muscles

C. Atrial contraction

II. Ventricular Afterload

- A. Systemic vascular resistance
- B. Elasticity of arterial tree
- C. Arterial blood volume
- D. Ventricular wall tension
 - 1. Ventricular radius
 - 2. Ventricular wall thickness

III. Myocardial Contractility^a

- A. Intramyocardial $[Ca^{2+}] \uparrow \downarrow$
- B. Cardiac adrenergic nerve activity $\uparrow \downarrow^b$
- C. Circulating catecholamines $\uparrow \downarrow^b$
- D. Cardiac rate $\uparrow \downarrow^b$
- E. Exogenous inotropic agents $\uparrow$
- F. Myocardial ischemia $\downarrow$
- G. Myocardial cell death (necrosis, apoptosis, autophagy) $\downarrow$
- H. Alterations of sarcomeric and cytoskeletal proteins $\downarrow$
 - 1. Genetic
 - 2. Hemodynamic overload
- I. Myocardial fibrosis $\downarrow$
- J. Chronic overexpression of neurohormones $\downarrow$
- K. Ventricular remodeling $\downarrow$
- L. Chronic and/or excessive myocardial hypertrophy $\downarrow$

^aArrows indicate directional effects of determinants of contractility. ^bContractility rises initially but later becomes depressed.

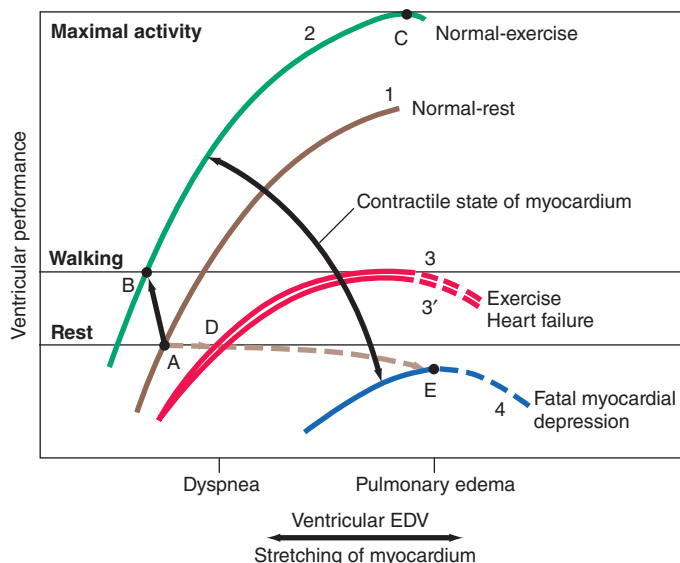


FIGURE 244-9 The interrelations among influences on ventricular end-diastolic volume (EDV) through stretching of the myocardium and the contractile state of the myocardium. Levels of ventricular EDV associated with filling pressures that result in dyspnea and pulmonary edema are shown on the abscissa. Levels of ventricular performance required when the subject is at rest, while walking, and during maximal activity are designated on the ordinate. The broken lines are the descending limbs of the ventricular-performance curves, which are rarely seen during life but show the level of ventricular performance if end-diastolic volume could be elevated to very high levels. For further explanation, see text. (Reproduced with permission from WS Colucci, and E Braunwald: *Pathophysiology of heart failure*, in Braunwald's *Heart Disease*, 7th ed, Philadelphia: Elsevier, 2005.)

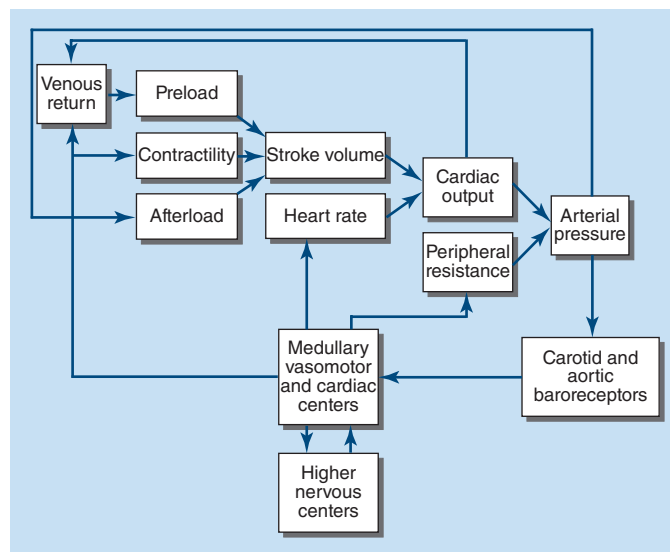


FIGURE 244-10 Interactions in the intact circulation of preload, contractility, and afterload in producing stroke volume. Stroke volume combined with heart rate determines cardiac output, which, when combined with peripheral vascular resistance, determines arterial pressure for tissue perfusion. The characteristics of the arterial system also contribute to afterload, an increase that reduces stroke volume. The interaction of these components with carotid and aortic arch baroreceptors provides a feedback mechanism to higher medullary and vasomotor cardiac centers and to higher levels in the central nervous system to effect a modulating influence on heart rate, peripheral vascular resistance, venous return, and contractility. (Reproduced with permission from MR Starling: *Physiology of myocardial contraction*, in *Atlas of Heart Failure: Cardiac Function and Dysfunction*, 3rd ed, WS Colucci and E Braunwald [eds]. Philadelphia: Current Medicine; 2002.)

■ EXERCISE

The integrated response to exercise illustrates typical interactions among the three determinants of stroke volume: preload, afterload, and contractility (Fig. 244-9). Hyperventilation, the pumping action of the exercising muscles, and venoconstriction during exercise all augment venous return and hence ventricular filling and preload (Table 244-2). Simultaneously, the increase in neuronal and humoral adrenergic stimulation of the myocardium and the tachycardia that occur during exercise combine to augment the myocardial contractility (Fig. 244-9, curves 1 and 2), together elevating stroke volume and stroke work, with little or no change in end-diastolic pressure and volume (Fig. 244-9, points A and B). Vasodilation occurs in the exercising muscles, thus limiting the increase in afterload that otherwise would occur as cardiac output rises to levels as high as five times greater than basal levels during maximal exercise. This vasodilation ultimately allows the achievement of elevated cardiac outputs during exercise at arterial pressures only moderately higher than the resting state.

ASSESSMENT OF CARDIAC FUNCTION

Several techniques can define impaired cardiac function in clinical practice. Cardiac output and stroke volume may decline in the presence of heart failure, but these variables are often within normal limits, especially at rest, even late in disease. A more sensitive index of cardiac function is the ejection fraction, i.e., the ratio of stroke volume to end-diastolic volume (normal value = $67 \pm 8\%$), which is frequently depressed in systolic heart failure even when stroke volume is normal. Alternatively, abnormally elevated ventricular end-diastolic volume (normal value = $75 \pm 20 \text{ mL/m}^2$) or end-systolic volume (normal value = $25 \pm 7 \text{ mL/m}^2$) signifies left ventricular systolic impairment.

Noninvasive techniques, particularly echocardiography, radionuclide scintigraphy, and cardiac magnetic resonance imaging (MRI) (Chap. 248), have great value in the clinical assessment of myocardial function. They provide measurements of end-diastolic and end-systolic volumes, ejection fraction, and systolic shortening rate, and they allow assessment of ventricular filling (see below) as well as regional contraction, relaxation, and tissue characterization. The latter measurements

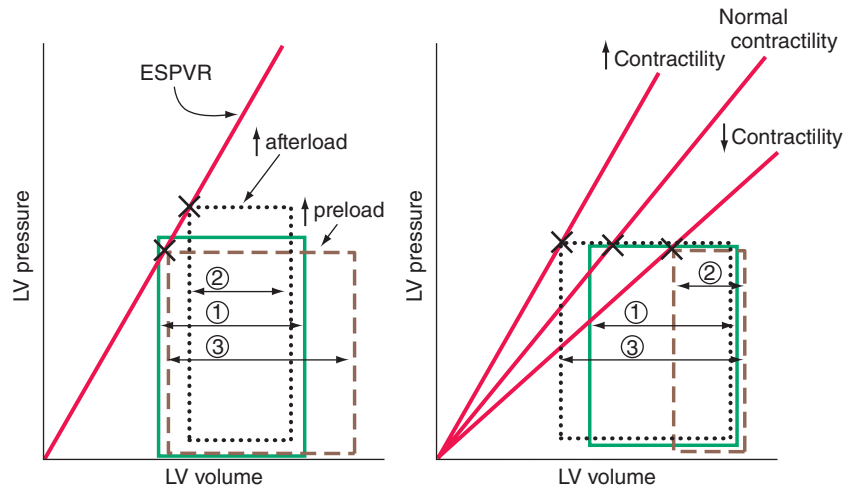


FIGURE 244-11 The responses of the left ventricle to increased afterload, increased preload, and increased and reduced contractility are shown in the pressure-volume plane. **Left.** Effects of increases in preload and afterload on the pressure-volume loop. Because there has been no change in contractility, the end-systolic pressure-volume relationship (ESPVR) is unchanged. With an increase in afterload, stroke volume falls (1 → 2); with an increase in preload, stroke volume rises (1 → 3). **Right.** With increased myocardial contractility and constant left ventricular end-diastolic volume, the ESPVR moves to the left of the normal line (lower end-systolic volume at any end-systolic pressure) and stroke volume rises (1 → 3). With reduced myocardial contractility, the ESPVR moves to the right; end-systolic volume is increased, and stroke volume falls (1 → 2).

have particular importance in ischemic heart disease, as myocardial infarction causes regional myocardial damage.

Strong dependence on ventricular loading conditions influences the precision of measurements of cardiac output, ejection fraction, and ventricular volumes as indices of cardiac function. Thus, a depressed ejection fraction and lowered cardiac output may occur in patients with normal ventricular function but reduced preload, as occurs in hypovolemia, or with increased afterload, as occurs in acutely elevated arterial pressure.

The end-systolic left ventricular pressure-volume relationship has particular value as an index of ventricular performance as it does not depend on preload and afterload (Fig. 244-11). At any level of myocardial contractility, left ventricular end-systolic volume varies inversely with end-systolic pressure; as contractility declines, end-systolic volume (at any level of end-systolic pressure) rises. Invasive measurement of end-systolic left ventricular pressure-volume loops adds rigor to research studies of left ventricular function, but these techniques are less pragmatic than the more readily assessed indices obtained in routine clinical practice, such as ventricular volumes and ejection fraction. Integrated cardiopulmonary exercise testing with formal analysis of exhaled gases is now more broadly available and can estimate maximal oxygen delivery as an indirect metric of physiologic reserve. Longitudinal measurements of some aspects of cardiovascular physiology are increasingly feasible with implantable or wearable devices.

DIASTOLIC FUNCTION

Ventricular filling is influenced by several characteristics of the myocardium including: (1) the extent and speed of myocardial relaxation; and (2) the passive stiffness of the ventricular wall. The former is largely a function of the rate of uptake of Ca^{2+} by the SR that may be enhanced by adrenergic activation and reduced by ischemia due to limited ATP available for pumping Ca^{2+} into the SR (see above). For the latter, ventricular stiffness increases with hypertrophy, fibrosis, and conditions that infiltrate the ventricle, such as amyloid, or can result from an extrinsic constraint (e.g., pericardial constriction) (Fig. 244-12).

Ventricular filling can be assessed by measuring flow velocity across the mitral valve using Doppler ultrasound. Normally, inflow velocity is more rapid in early diastole than during atrial systole. However, with mild to moderately impaired relaxation, the rate of early diastolic filling declines, as presystolic filling rates rise. With further stiffening, flow is “pseudo-normalized,” as early ventricular filling becomes more rapid with rising left atrial pressure upstream of the left ventricle.

CARDIAC METABOLISM

The heart requires a continuous supply of energy (ATP) not only to drive mechanical contraction, but also to maintain ionic and biochemical homeostasis. The development of tension, the frequency of contraction, and myocardial contractility levels are the principal determinants of the heart's energy and oxygen requirements, representing ~15% of that of the entire organism.

The heart's ATP production requires the generation of acetyl coenzyme A that can be derived from (in descending order) free fatty acids (FFAs), glucose, lactate, amino acids, and ketone bodies. Myocardial FFAs derive from circulating FFAs, whereas the cardiomyocyte's glucose derives from plasma as well as from myocardial glycogen stores (via glycogenolysis). These two principal sources of acetyl coenzyme

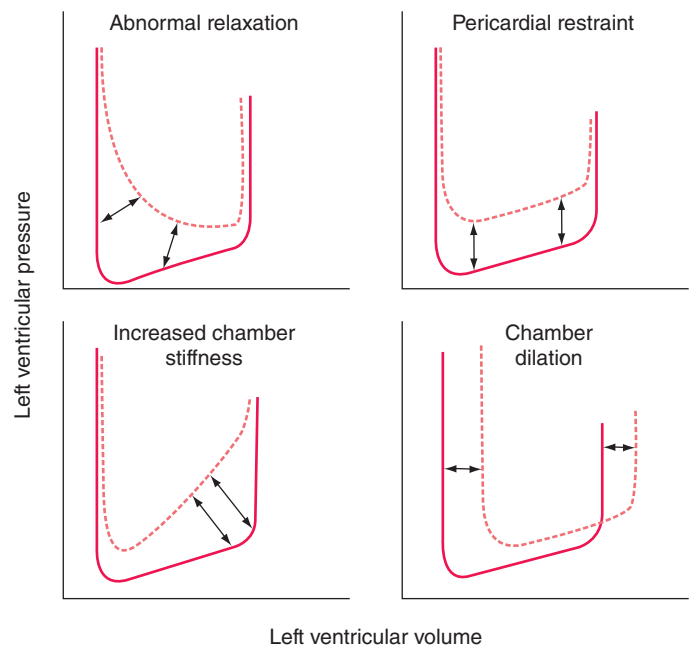


FIGURE 244-12 Mechanisms that cause diastolic dysfunction reflected in the pressure-volume relation. The bottom half of the pressure-volume loop is depicted. Solid lines represent normal subjects; broken lines represent patients with diastolic dysfunction. (Reproduced with permission from JD Carroll et al: The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. *Circulation*; 1986; 74: 815.)

A are metabolized distinctly in cardiac muscle. Glucose is converted in the cytoplasm into pyruvate, which passes into mitochondria for conversion into acetyl-CoA that then undergoes oxidation. FFAs are converted to acyl-CoA in the cytoplasm and acetyl-CoA in the mitochondria. Acetyl-CoA enters the citric acid (Krebs) cycle to produce ATP by oxidative phosphorylation; ATP then enters the cytoplasm from the mitochondrial compartment. Intracellular adenosine diphosphate (ADP), resulting from ATP breakdown, enhances ATP production.

In the fasted, resting state, circulating FFAs furnish most of the heart's acetyl-CoA (~70%). In the fed state, with elevations of blood glucose and insulin, glucose oxidation increases and FFA oxidation subsides. Increased cardiac work, inotropic agents, hypoxia, and mild ischemia all enhance myocardial glucose uptake, production (glycogenolysis), and metabolism to pyruvate (glycolysis). Exercise raises circulating lactate levels and myocardial utilization of acetyl-CoA. By contrast, β -adrenergic stimulation raises the circulating levels and metabolism of FFAs in favor of glucose. Severe myocardial ischemia inhibits cytoplasmic pyruvate dehydrogenase, producing incomplete glucose metabolism to lactic acid (anaerobic glycolysis). Anaerobic glycolysis produces much less ATP per mole of glucose than does aerobic glucose metabolism. High concentrations of circulating FFAs, which can occur when adrenergic stimulation is superimposed on severe ischemia, reduce oxidative phosphorylation, and the myocardial content of ATP declines, impairing contraction. In addition, FFA breakdown products may exert toxic or arrhythmogenic effects on cardiac cell membranes.

Myocardial energy is stored as creatine phosphate (CP), which is in equilibrium with ATP, the immediate energy source. In states of reduced energy availability, the CP stores decline first. Cardiac hypertrophy, fibrosis, tachycardia, increased wall tension due to ventricular dilation, and increased intracytoplasmic $[Ca^{2+}]$ all contribute to increased myocardial energy needs. When coupled with reduced coronary flow reserve, as occurs with obstruction of coronary arteries or abnormalities of the coronary microcirculation, an imbalance in myocardial ATP production relative to demand may occur, and the resulting ischemia can worsen or cause heart failure.

■ CARDIAC CELLULAR INTERVENTIONS: REGENERATION AND REPAIR

Adult mammalian myocardial cells are fully differentiated and have little or no regenerative potential; however, there is evidence that the immature mammalian heart has some limited regenerative potential that rapidly becomes constrained with increasing maturity and workload. Considerable current effort is being devoted to evaluating the utility of various approaches to facilitate the transient release of these constraints on regeneration to enhance cardiac repair after injury. Recent work has also shown that by engineering chimeric antigen receptors on T lymphocytes (CAR-T), it may be possible to reverse fibrosis in the heart. The success of such approaches would offer the exciting possibility of reconstructing an infarcted or failing ventricle.

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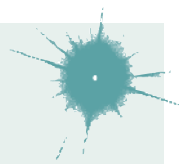
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245

Epidemiology of Cardiovascular Disease

J. Michael Gaziano, Thomas A. Gaziano



Cardiovascular disease (CVD) is now the most common cause of death worldwide. Before 1900, infectious diseases and malnutrition were the most common causes, and CVD was responsible for <10% of all deaths. In 2022, CVD accounted for over 19 million deaths worldwide (33%), with the same rate now occurring in both high-income countries and low- and middle-income countries.

THE EPIDEMIOLOGIC TRANSITION

The global rise in CVD is the result of an unprecedented transformation in the causes of morbidity and mortality during the twentieth century. Known as the epidemiologic transition, this shift is driven by industrialization, urbanization, and associated lifestyle and demographic changes and is taking place in every part of the world among all races, ethnic groups, and cultures. The transition is divided into four basic stages: pestilence and famine, receding pandemics, degenerative and man-made diseases, and delayed degenerative diseases. A fifth stage, characterized by an epidemic of inactivity and obesity, is emerging in many countries that have moderate economic development (**Table 245-1**).

The *age of pestilence and famine* is marked by malnutrition, infectious diseases, and high infant and child mortality that are offset by high fertility. Tuberculosis, dysentery, cholera, and influenza are often fatal, resulting in a mean life expectancy of about 30 years. CVD, which accounts for <10% of deaths, takes the form of rheumatic heart disease and cardiomyopathies due to infection and malnutrition. Despite advances in treatment of those with rheumatic heart disease, incidence and prevalence rates increased between 1990 and 2019.

Per capita income and life expectancy increase during the *age of receding pandemics* as the emergence of public health systems, cleaner water supplies, and improved nutrition combine to drive down deaths from infectious disease and malnutrition. Infant and childhood mortality also decline, but deaths due to CVD increase to between 10 and 35% of all deaths. Rheumatic valvular disease, hypertension, coronary heart disease (CHD), and stroke are the predominant forms of CVD. Almost 40% of the world's population is currently in this stage.

The *age of degenerative and man-made diseases* is distinguished by mortality from noncommunicable diseases—primarily CVD—surpassing mortality from malnutrition and infectious diseases. Caloric intake, particularly from animal fat, increases. CHD and stroke are prevalent, and between 35 and 65% of all deaths can be traced to CVD. Typically, the rate of CHD deaths exceeds that of stroke by a ratio of 2:1 to 3:1. During this period, average life expectancy surpasses the age of 50. Roughly 35% of the world's population falls into this category.

In the *age of delayed degenerative diseases*, CVD and cancer remain the major causes of morbidity and mortality, with CVD accounting for 40% of all deaths. However, age-adjusted CVD mortality declines, aided by preventive strategies (for example, smoking cessation programs and effective blood pressure control), acute hospital management, and technologic advances, such as the availability of bypass

TABLE 245-1 Five Stages of the Epidemiologic Transition

STAGE	DESCRIPTION	DEATHS RELATED TO CVD, %	PREDOMINANT CVD TYPE
Pestilence and famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths related to malnutrition and infection; precipitous decline in infant and child mortality rates	10–35	Rheumatic valvular disease, hypertension, CHD, and stroke (predominantly hemorrhagic)
Degenerative and man-made diseases	Increased fat and caloric intake and decrease in physical activity lead to emergence of hypertension and atherosclerosis; with increase in life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious disease	35–65	CHD and stroke (ischemic and hemorrhagic)
Delayed degenerative diseases	CVD and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events; age-adjusted CVD mortality declines; CVD affecting older and older individuals	40–50	CHD, stroke, and congestive heart failure
Inactivity and obesity	Overweight and obesity increase at alarming rate; diabetes and hypertension increase; decline in smoking rates levels off; a minority of the population meets physical activity recommendations	<40	CHD, stroke, and congestive heart failure, peripheral vascular disease

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.

Source: Data from AR Omran: The epidemiologic transition: A theory of the epidemiology of population change. *Milbank Mem Fund Q* 49:509, 1971; and SJ Olshansky, AB Ault: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. *Milbank Q* 64:355, 1986.

surgery. CHD, stroke, and congestive heart failure are the primary forms of CVD. About 15% of the world's population is now in the age of delayed degenerative diseases or is exiting this age and moving into the fifth stage of the epidemiologic transition.

In the industrialized world, physical activity continues to decline while total caloric intake increases. The resulting epidemic of overweight and obesity may signal the start of the *age of inactivity and obesity*. Rates of type 2 diabetes mellitus, hypertension, and lipid abnormalities are on the rise, trends that are particularly evident in children. As these risk factor trends continue, age-adjusted CVD mortality rates that have fallen for decades during the fourth phase have started to increase in recent years during this fifth phase.

■ PATTERNS IN THE EPIDEMIOLOGIC TRANSITION

Unique regional features have modified aspects of the transition in various parts of the world. High-income countries experienced declines in CVD death rates by as much as 50–60% over the past 60 years, whereas CVD deaths increased by 15% over the past 20 years in the low- and middle-income range and the rate of change has been faster. However, given the large amount of available data, the United States serves as a useful reference point for comparisons. The age of pestilence and famine occurred before 1900, with a largely agrarian economy and population. Infectious diseases accounted for more deaths than any other cause. By the 1930s, the country proceeded through the age of receding pandemics. The establishment of public health infrastructures resulted in dramatic declines in infectious disease mortality rates. Lifestyle changes due to rapid urbanization resulted in a simultaneous increase in CVD mortality rates, reaching ~390 per 100,000. Between 1930 and 1965, the country entered the age of degenerative and man-made diseases. Infectious disease mortality rates fell to fewer than 50 per 100,000 per year, whereas CVD mortality rates reached peak levels with increasing urbanization and lifestyle changes in diet, physical activity, and tobacco consumption. The age of delayed degenerative diseases took place between 1965 and 2000. New therapeutic approaches, preventive measures, and exposure to public health campaigns promoting lifestyle modifications led to substantial declines in age-adjusted mortality rates and a steadily rising age at which a first CVD event occurs.

Currently, the United States is entering what appears to be a fifth phase. The decline in the age-adjusted CVD death rate of 3% per year through the 1970s and 1980s has tapered off in the 1990s to 2% through 2010. There was then limited reduction in the 2010–2019 period, and in 2020 and 2021, there was an increase in CVD mortality rates that had not been seen since the early 1960s. Competing trends appear to be at play. On the one hand, an increase in the prevalence of diabetes and obesity, a slowing in the rate of decline in smoking, and a leveling off

in the rate of detection and worsening treatment for hypertension are in the negative column. On the other hand, cholesterol levels continue to decline in the face of increased statin use.

Many high-income countries (HICs)—which together account for 15% of the population—have proceeded through four stages of the epidemiologic transition in roughly the same pattern as the United States. CHD is the dominant form of CVD in these countries, with rates that tend to be two- to fivefold higher than stroke rates. However, variations exist. Whereas North America, Australia, and central northwestern European HICs experienced significant increases then rapid declines in CVD rates, southern and central European countries experienced a more gradual rise and fall in rates. More specifically, central European countries (i.e., Austria, Belgium, and Germany) declined at slower rates compared to their northern counterparts (i.e., Finland, Sweden, Denmark, and Norway). Countries such as Portugal, Spain, and Japan never reached the high mortality rates that the United States and other countries did, with CHD mortality rates at 200 per 100,000, or less. The countries of Western Europe also exhibit a clear north/south gradient in absolute rates of CVD, with rates highest in northern countries (i.e., Finland, Ireland, and Scotland) and lowest in Mediterranean countries (i.e., France, Spain, and Italy). Japan is unique among the HICs, most likely due to the unique dietary patterns of its population. Although stroke rates increased dramatically, CHD rates did not rise as sharply in Japan. However, Japanese dietary habits are undergoing substantial changes, reflected in an increase in cholesterol levels.

Patterns in low- and middle-income countries (LMICs; gross national income per capita \$11,666) depend, in part, on cultural differences, secular trends, and responses at the country level, with regard to both public health and treatment infrastructure. Although communicable diseases continue to be a major cause of death, CVD has emerged as a significant health concern in LMICs. With 85% of the world's population, LMICs are driving the rates of change in the global burden of CVD (Fig. 245-1). In most LMICs, an urban/rural gradient has emerged for CHD, stroke, and hypertension, with higher rates in urban centers.

However, although CVD rates are rapidly rising globally, vast differences exist among the regions and countries, and even within the countries themselves (Fig. 245-2). The East Asia and Pacific regions appear to be fully in the third phases of the epidemiologic transition. CVD is a major cause of death in China, but like Japan, stroke causes more deaths than CHD in a ratio of about three to one. Vietnam and Cambodia, on the other hand, are just emerging from the pestilence and famine transition. The Middle East and North Africa regions also appear to be well into the third phase of the epidemiologic transition, with increasing life expectancy and CVD death rates just below those of HICs. In general, Latin America appears to be in the third phase of

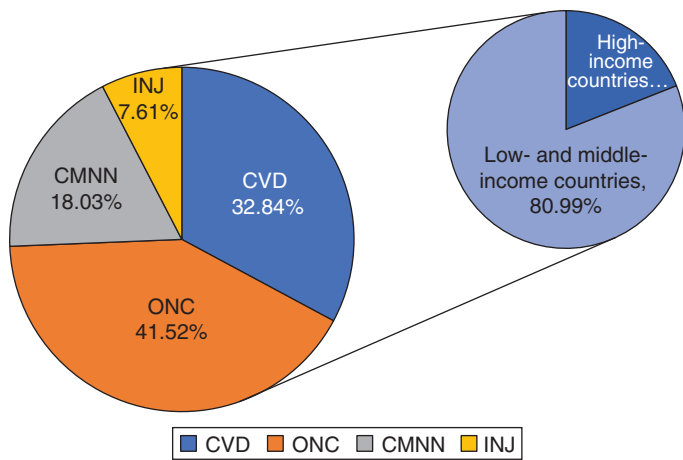


FIGURE 245-1 Global deaths by cause, 2019. CMNN, communicable, maternal, neonatal, and nutritional disorders; CVD, cardiovascular diseases; INJ, injuries; ONC, other noncommunicable diseases. (Based on data from *Global Burden of Disease Study 2017*. *Global Burden of Disease Study 2017 [GBD 2017] Results*. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2020.)

the transition, although there is vast regional heterogeneity with some areas in the second phase of the transition and more in the fourth. The Eastern Europe and Central Asia regions, however, are firmly in the peak of the third phase, with the highest death rates due to CVD (~55%) in the world. Importantly, deaths due to CHD are not limited to the elderly in this region and have a significant effect on working-age populations. South Asia—and more specifically, India, which accounts for the greatest proportion of the region's population—is experiencing an alarming increase in heart disease. The transition appears to be in the Western style, with CHD as the dominant form of CVD. However, rheumatic heart disease continues to be a major cause of morbidity and

mortality. As in South Asia, rheumatic heart disease is also an important cause of CVD morbidity and mortality in sub-Saharan Africa, which largely remains in the first phase of the epidemiologic transition.

Many factors contribute to this heterogeneity among LMICs. First, the regions are in various stages of the epidemiologic transition. Second, vast differences in lifestyle and behavioral risk factors exist. Third, racial and ethnic differences may lead to altered susceptibilities to various forms of CVD. In addition, it should be noted that for most countries in these regions, accurate country-wide data on cause-specific mortality are not complete.

GLOBAL TRENDS IN CARDIOVASCULAR DISEASE

Over the past 5 years, there have been changes in the trends of CVD that are reflective of both trends in demographics and management of disease, but also of the way deaths and diseases have been measured and estimated. In 2017, the Global Burden of Disease (GBD) Study updated its estimates with several important changes based on newly available data, refinement in the causes of death, and the introduction of new modeling techniques. The major changes include the addition of an independent estimation of population and fertility, the addition of over 127 country-years of vital registration and verbal autopsy data, revisions of some deaths from “misclassified” to dementia, Parkinson’s disease and atrial fibrillation, and the addition of new diseases such as nonrheumatic calcific aortic and degenerative mitral valve disease. CVD accounts for 32% of deaths worldwide, a number expected to increase. In 2019, CHD accounted for 16.2% of all deaths globally and the largest portion (10%) of global years of life lost (YLLs) and disability-adjusted life-years (DALYs) (7.2%). Stroke moved from the third to the second largest cause of death (11.6% of all deaths) and remained the third largest contributor to global YLLs (7.5%) and DALYs (5.7%). Together, CHD and stroke accounted for more than a quarter of all deaths worldwide. The burden of stroke is of growing concern among LMICs. The impact of stroke on DALYs and mortality rates is more than three times greater in LMICs as compared to HICs.

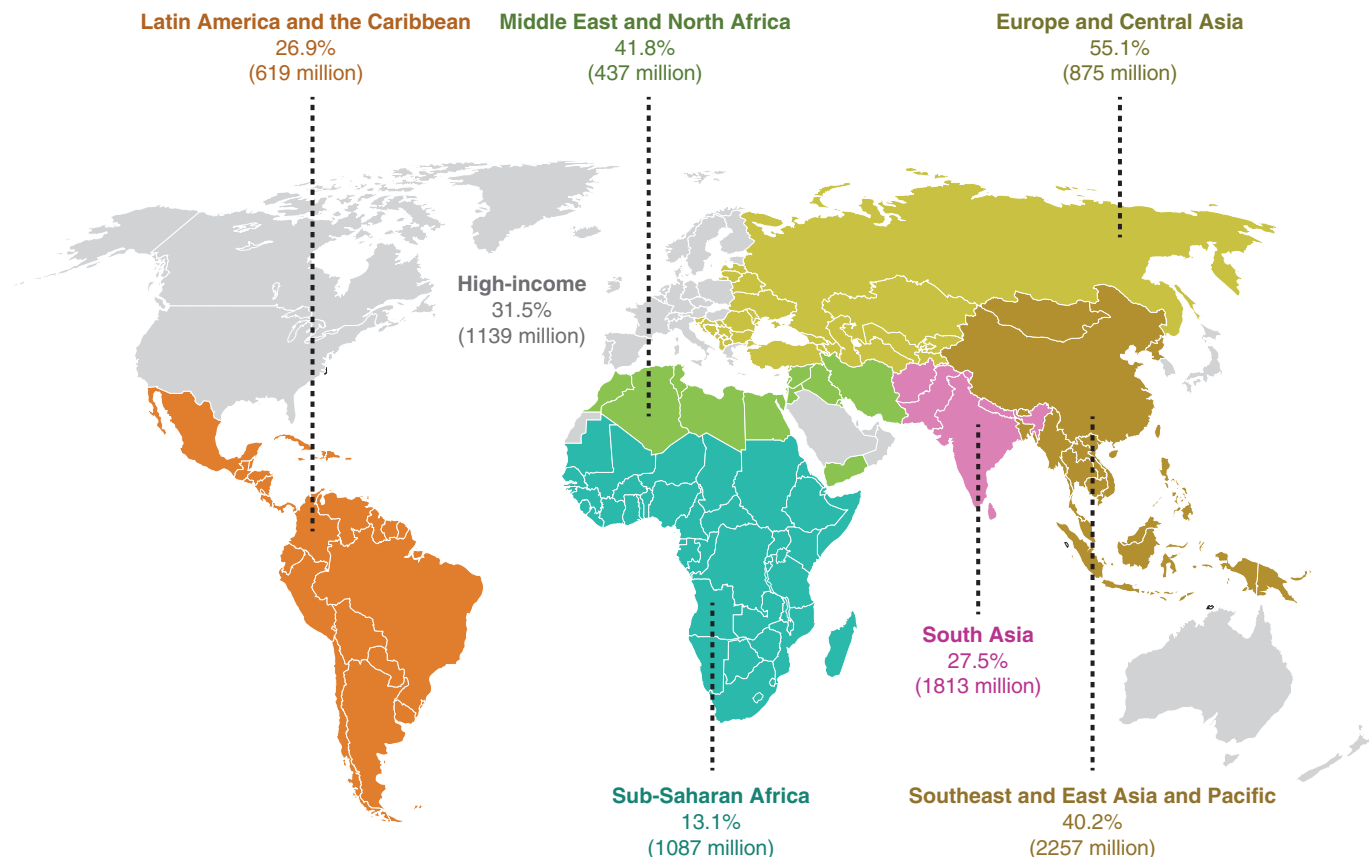


FIGURE 245-2 Cardiovascular disease deaths as a percentage of total deaths and total population in seven economic regions of the world defined by the World Bank. (Based on data from *Global Burden of Disease Study 2017*. *Global Burden of Disease Study 2019 [GBD 2019] Results*. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2023.)

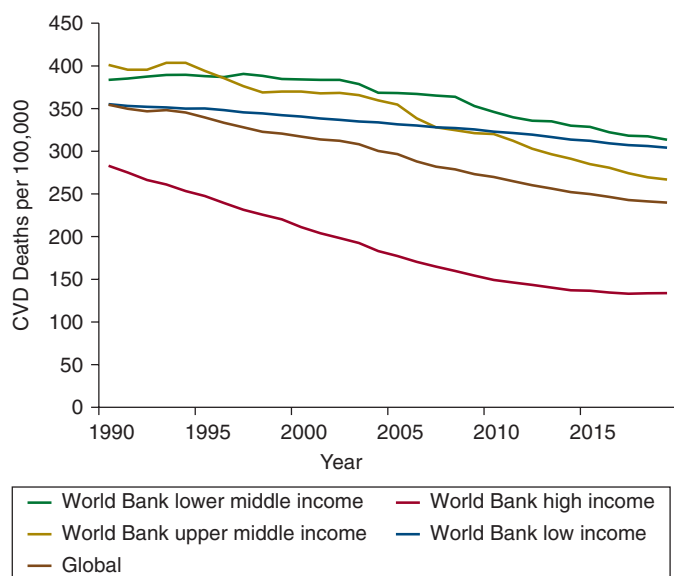


FIGURE 245-3 Age-standardized cardiovascular diseases (CVD) death rate per 100,000 from 1990 to 2019, by World Bank income. (Based on data from *Global Burden of Disease Study 2019*. *Global Burden of Disease Study 2019 [GBD 2019] Results*. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2023.)

With 85% of the world's population, LMICs largely drive global CVD rates and trends. More than 15 million CVD deaths occurred in LMICs in 2019, compared to 3.5 million in HICs. Globally, there is evidence of significant delays in age of occurrence and/or improvements in case fatality rates; between 1990 and 2019, the number of CVD deaths increased by 54%, but age-adjusted death rates decreased by 32.4% in the same period. Age-standardized death rates, however, have declined faster in HICs than in middle-income and lower-income regions (Fig. 245-3). Population growth has been greater in LMICs compared to HICs. As a result of slower rates of population growth in HICs, overall CVD deaths remained steady. However, in the LMICs, the population aging and growth outstripped gains in age-adjusted mortality reductions such that overall CVD deaths continued to climb over the past 25 years (Fig. 245-4).

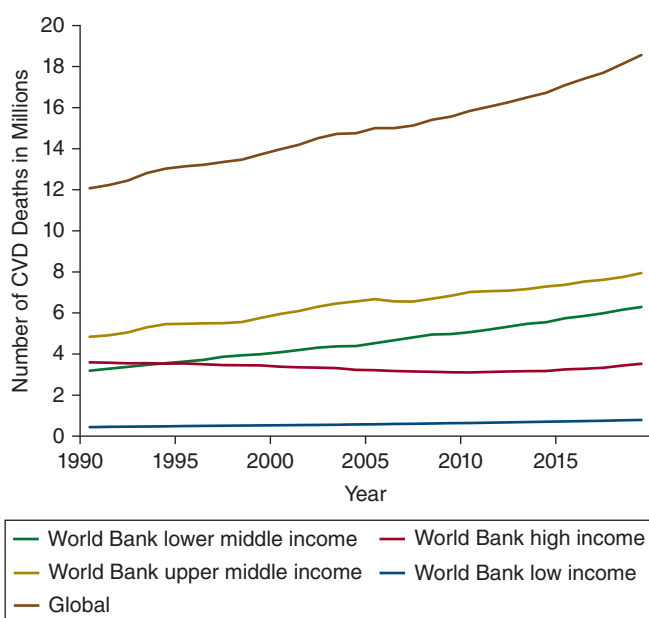


FIGURE 245-4 Number of cardiovascular diseases (CVD) deaths from 1990 to 2019, by World Bank income. (Based on data from *Global Burden of Disease Study 2019*. *Global Burden of Disease Study 2019 [GBD 2019] Results*. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2023.)

Although HIC population growth will be fueled by immigration from LMICs, the populations of HICs will shrink as a proportion of the world's population. The modest decline in CVD death rates that began in the HICs in the latter third of the twentieth century will continue, but the rate of decline appears to be slowing. However, these countries are expected to see an increase in the prevalence of CVD, as well as the absolute number of deaths as the population ages.

Significant portions of the population living in LMICs have entered the third phase of the epidemiologic transition, and some are entering the fourth stage. Changing demographics play a significant role in future predictions for CVD throughout the world. For example, the population in Eastern Europe declined by 3% between 2010 and 2023, whereas it grew by 30% in South Asia. CVD rates will also have an economic impact. Even assuming no increase in CVD risk factors, most countries, but especially India and South Africa, will see a large number of people between 35 and 64 die of CVD over the next 30 years, as well as an increasing level of morbidity among middle-aged people related to heart disease and stroke.

RISK FACTORS

Global variation in CVD rates is related to temporal and regional variations in known risk factors and behaviors. Ecologic analyses of major CVD risk factors and mortality demonstrate high correlations between expected and observed mortality rates for the three main risk factors—smoking, serum cholesterol, and hypertension—and suggest that many regional variations are based on differences in conventional risk factors.

Behavioral Risk Factors • TOBACCO Over 1.3 billion people use tobacco worldwide. Tobacco use currently causes about 8.7 million deaths annually (15.4% of all deaths), 3.2 million of which are CVD related. The population of the HIC group smokes (21.6%) at almost double the rate of the low-income countries (11.2%), whereas the middle-income country group's smoking rate (19.5%) approximates the global average (22.3%). From 2007 to 2017, smoking rates decreased across low-, middle-, and high-income country groups, with relative reductions of 19%, 12%, and 20%, respectively. By 2030, the global average smoking rate is expected to decline from 19% to 16% (women, 4%; men, 28%); however, the number of tobacco users is expected to rise owing to population growth. Secondhand smoke is another well-established cause of CVD, responsible for 598,000 CVD deaths of nonsmokers in 2019. Although smoking bans have both immediate and long-term benefits, implementation varies greatly between countries.

DIET Total caloric intake per capita increases as countries develop. With regard to CVD, a key element of dietary change is an increase in intake of saturated animal fats and hydrogenated vegetable fats, which contain atherogenic *trans* fatty acids, along with a decrease in intake of plant-based foods and an increase in simple carbohydrates. Fat contributes <20% of calories in rural China and India, <30% in Japan, and over 35% in the United States. Caloric contributions from fat appear to be increasing in the United States but falling in the other HICs.

PHYSICAL INACTIVITY The increased mechanization that accompanies the economic transition leads to a shift from physically demanding, agriculture-based work to largely sedentary industry- and office-based work. Physical inactivity is responsible for 1.3 million global deaths in 2019. The global prevalence of physical inactivity has remained steady between 2001 and 2016 (28.5% to 27.5%). Mortality rates attributable to inactivity are highest in North Africa and the Middle East and in Central and Eastern Europe and lowest in sub-Saharan Africa.

METABOLIC RISK FACTORS

Examination of trends in metabolic risk factors provides insight into changes in the CVD burden globally. Here we describe four metabolic risk factors—lipid levels, hypertension, obesity, and diabetes mellitus—using data from the *Global Burden of Disease, Injuries, and Risk Factors Study (GBD 2019)*. The GBD project identified and compiled mortality and morbidity data from 195 countries from 1980 to 2017.

Lipid Levels Worldwide, high low-density lipoprotein cholesterol levels are estimated to play a role in 41% of ischemic heart disease deaths and 9% of stroke deaths, amounting to 4 million deaths in 2019. Although mean population plasma cholesterol levels tend to rise as countries move through the epidemiologic transition, mean serum total cholesterol levels have decreased globally between 1980 and 2008 by 0.08 mmol/L per decade in men and 0.07 mmol/L per decade in women. Large declines occurred in Australasia, North America, and Western Europe (0.19–0.21 mmol/L). Countries in the East Asia and Pacific region experienced increases of >0.08 mmol/L in both men and women. More recent research including Mendelian studies suggests that lipoprotein(a) may act as an individual predictor of CVD risk beyond traditional total or low-density lipoprotein cholesterol through increased cellular lipid accumulation, endothelial dysfunction, and impacts on coagulation. It appears to be elevated in ~20% of the global population, although fewer data are available from LMICs. Non-randomized data suggest higher rates among those of African descent with twice the levels of Caucasians, with East Asians and South Asians having intermediate levels. There are limited clinical trial data on clinical agents that target lipoprotein(a), although PCSK9 inhibitors lower it or other specific targets, so this remains an area of intense research.

Hypertension Elevated blood pressure is an early indicator of the epidemiologic transition. Observational studies show increased risk of CVD beginning with systolic blood pressures (SBPs) >110–115 mmHg. Between 1990 and 2015, the global prevalence of SBP ≥110–115 mmHg increased from 73,119 to 81,373 per 100,000, whereas the prevalence of SBP ≥140 mmHg rose from 17,307 to 20,526 per 100,000. In 2015, of the estimated 3.47 billion adults with SBP ≥110–115 mmHg, 874 million (25%) had SBP ≥140 mmHg. While SBP ≥140 mmHg accounts for only 25% of those with elevated blood pressure, it accounted for 73% (7.8 million) of deaths due to SBP of ≥110–115 mmHg in 2015. Worldwide, 53% of stroke deaths (3.44 million) and 53% of CHD deaths (4.86 million) are attributable to high blood pressure, accounting for 10.8 million deaths in 2019. From 1990 to 2015, the number of deaths related to SBP ≥140 mmHg increased in all LMIC groups but fell in HICs. Between 1980 and 2008, the age-standardized prevalence of uncontrolled hypertension decreased even as the number of people with uncontrolled hypertension increased due to population growth and aging. However, concerning trends of declining hypertension control rates were seen in the United States since 2016 with many middle-income countries now outperforming high-income nations. Rising mean population blood pressure also occurs as populations industrialize and move from rural to urban settings. For example, the prevalence of hypertension in urban India is 33.8%, but varies between 14.5 and 31.7% in rural regions. One major concern in LMICs is the high rate of undetected, and therefore untreated, hypertension. This may explain, at least in part, the higher stroke rates in these countries in relation to CHD rates during the early stages of the transition. The high rates of hypertension throughout Asia, especially undiagnosed hypertension, likely contribute to the high prevalence of hemorrhagic stroke in the region.

Obesity In 2025, an estimated 892 million adults will be obese. Global obesity prevalence is projected to be 16.1% among adults and is increasing throughout the world, particularly in developing countries where the trajectories are steeper than those experienced by the developed countries. High body mass index (BMI) contributed to 5.0 million deaths worldwide (7.1% deaths from any cause); CVD was the leading cause of these deaths (1.95 million) and also of associated DALYs (160 million) followed by diabetes (0.6 million deaths, 30.4 million DALYs). Women are more affected by obesity than men; from 1975 to 2014, global mean age-standardized BMI increased from 22.1 to 24.4 kg/m² in females and from 21.7 to 24.2 kg/m² in males, whereas the prevalence of obesity increased from 6.4% to 14.9% in females and 3.2% to 10.8% in males. The proportion of the world's adult women who are either overweight or obese rose from 29.8% to 38.0% between 1980 and 2013, while an increase from 28.8% to 36.9% was observed for men. Country and regional differences are observed. The highest prevalence of male obesity is in the United States, Southern and Central

Latin America, Australasia, and Central and Western Europe. For females, the highest prevalence of obesity is in Southern and North Africa, the Middle East, Central and Southern Latin America, and the United States. The lowest prevalence for both males and females was observed in South and Southeast Asia and in East, Central, and West Africa.

Diabetes Mellitus As a consequence of, or in addition to, increasing BMI and decreasing levels of physical activity, worldwide rates of diabetes—predominantly type 2 diabetes—are on the rise. According to the most recent data from the GBD project, the prevalence of diabetes increased 129.7% for males and 120.9% for females between 1990 and 2017. An estimated 476 million people worldwide have diabetes, and the International Diabetes Foundation predicts this number will reach 693 million by 2045. Nearly 50% of people with diabetes are undiagnosed, and 80% live in LMICs. The Middle East and North Africa have the highest regional age-standardized prevalence (8.7% of the population) and incidence rates (400 per 100,000) of diabetes, whereas East Asia and the Pacific have the lowest (5.8%; 249 per 100,000). Future growth will also largely occur in the Middle East and Africa, along with other LMICs in South Asia and sub-Saharan Africa.

COVID-19 The impact of COVID-19 on CVD was significant. First, patients with acute conditions were hesitant to present to hospitals for fear of infection, resulting in delayed presentation for those with acute coronary syndrome (ACS) or stroke and missing critical early care. Additionally, even those who presented with ACS had worse outcomes sometimes related to testing delays. Furthermore, the presence of obesity and/or diabetes mellitus worsened outcomes. Finally, control rates of hypertension and dyslipidemia may have been exacerbated due to difficulty of access to providers.

■ GENETIC RISK FACTORS

A great deal of effort has recently been invested in understanding how genes affect cardiovascular health in populations. These efforts have focused on germline genetic variants that are related to specific CVDs as well as those that are associated with cardiovascular risk factors. In both cases, every year, the number of associated variants has increased meaningfully to the point that it appears that hundreds or even thousands of variants are associated with these conditions, each explaining a small amount of the population variability in disease and risk factors. Collections of variants have been combined in polygenic risk scores, but these too explain only a small amount of the variability of the disease in the population. Much more data will emerge in the coming years about these associations, the mechanisms that explain these associations, the relationships of variants that are specific to certain tissues such as the heart or the brain, and the interactions between genetic and lifestyle factors in causing disease. Currently, most of the data are among those with European ancestry; however, large-scale efforts are underway to understand the relationships between genes and diseases and their risk factors around the world. The early data suggest non-trivial differences among various world populations. Beyond germline risk, there appears to be increased cardiovascular risk associated with age-related expansion of hematopoietic clones with somatic mutations, including loss-of-function alleles of certain genes. Individuals with these mutations without other hematologic abnormalities are defined as having clonal hematopoiesis of indeterminate potential (CHIP). Recent studies suggest those with CHIP have up to a twofold increased risk of developing CHD.

SUMMARY

Although CVD rates are declining in the HICs, they are increasing in many other regions of the world. The consequences of this preventable epidemic will be substantial on many levels, including individual mortality and morbidity, family suffering, and staggering economic costs.

Three complementary strategies can be used to lessen the impact. First, the overall burden of CVD risk factors can be lowered through population-wide public health measures, such as national campaigns against cigarette smoking, unhealthy diets, and physical inactivity. Second, it is important to identify higher risk subgroups of the population

who stand to benefit the most from specific, low-cost prevention interventions, including screening for and treatment of hypertension and elevated cholesterol. Simple, low-cost interventions, such as the “polypill”—a regimen of aspirin, a statin, and an antihypertensive agent—now show trial data with reductions in events for both primary and secondary prevention and have been added to the WHO Essential Medicines list. Third, resources should be allocated to acute, as well as secondary, prevention interventions. For countries with limited resources, a critical first step in developing a comprehensive plan is better assessment of cause-specific mortality and morbidity, as well as the prevalence, of the major preventable risk factors.

In the meantime, the HICs must continue to bear the burden of research and development aimed at prevention and treatment, being mindful of the economic limitations of many countries. The concept of the epidemiologic transition provides insight into how to alter the course of the CVD epidemic. The efficient transfer of low-cost preventive and therapeutic strategies could alter the natural course of this epidemic and thereby reduce the excess global burden of preventable CVD.

FURTHER READING

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CLERKIN KJ et al: COVID-19 and cardiovascular disease. *Circulation* 141:1648, 2020.

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severity of cardiovascular disease even when the examination findings imply a low pretest probability of significant pathology. Proponents of the use of hand-held ultrasound devices to identify and characterize structural cardiac disease have called for its incorporation into educational curricula. Techniques to improve competency in bedside examination skills include repetition, patient-centered teaching conferences, visual display feedback of auscultatory events using Doppler echocardiographic imaging, and simulation-based training. The use of digital stethoscopes may enhance learning and is foundational to the application of computer- or artificial intelligence-assisted evaluation of auscultatory events.

The findings from the history and physical examination can help establish the presence, severity, and prognosis of several cardiovascular diseases. For example, observations regarding heart rate and blood pressure, signs of pulmonary congestion, and the presence of mitral regurgitation (MR) contribute importantly to bedside risk assessment in patients with acute coronary syndromes and can inform clinical decision-making before the results of cardiac biomarker testing are known. The prognosis of patients with heart failure can be predicted on the basis of the jugular venous pressure (JVP) and the presence or absence of a third heart sound (S_3). Accurate characterization of cardiac murmurs provides important insight into the natural history of many valvular and congenital heart lesions. Finally, the important role played by the physical examination in enhancing the clinician-patient relationship cannot be overstated.

THE GENERAL PHYSICAL EXAMINATION

The examination begins with an assessment of the general appearance of the patient, with notation of age, posture, demeanor, and overall health status. Is the patient in pain or resting quietly, dyspneic or diaphoretic? Does the patient choose to avoid certain body positions to reduce or eliminate pain, as might be the case with suspected acute pericarditis? Are there clues indicating that dyspnea may have a pulmonary cause, such as a barrel chest deformity with an increased anterior-posterior diameter, tachypnea, and pursed-lip breathing? Skin pallor, cyanosis, and jaundice can be appreciated readily and provide additional clues. The appearance of a chronically ill-appearing emaciated patient may suggest the presence of long-standing heart failure or another systemic disorder, such as a malignancy. Various genetic syndromes, often with cardiovascular involvement, can also be recognized easily, such as trisomy 21, Marfan syndrome, and Holt-Oram syndrome. Height and weight should be measured routinely, and both body mass index and body surface area should be calculated. Knowledge of the waist circumference and the waist-to-hip ratio can be used to predict long-term cardiovascular risk. Mental status, level of alertness, and mood should be assessed continuously during the interview and examination.

Skin Central cyanosis occurs with significant right-to-left shunting at the level of the heart or lungs, allowing deoxygenated blood to reach the systemic circulation. Peripheral cyanosis or acrocyanosis, in contrast, is usually related to reduced extremity blood flow due to small vessel constriction, as seen in patients with severe heart failure, shock, or peripheral vascular disease; it can be aggravated by the use of β -adrenergic blockers with unopposed α -mediated vasoconstriction. Differential cyanosis refers to isolated cyanosis affecting the lower but not the upper extremities in a patient with a large patent ductus arteriosus (PDA) and secondary pulmonary hypertension with right-to-left to shunting at the great vessel level. Telangiectasias on the lips, tongue, and mucous membranes, as part of the Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia), resemble spider nevi and can be a source of right-to-left shunting when also present in the lung. Malar telangiectasias also are seen in patients with advanced mitral stenosis (MS) or scleroderma. An unusually tan or bronze discoloration of the skin may suggest hemochromatosis as the cause of the associated systolic heart failure. Jaundice, which may be visible first in the sclerae, has a broad differential diagnosis but, in the appropriate setting, can be consistent with advanced right heart failure and congestive hepatomegaly. Various hereditary lipid disorders sometimes are associated with

Section 2 Diagnosis of Cardiovascular Disorders

246 Physical Examination of the Cardiovascular System

Patrick T. O’Gara, Joseph Loscalzo

The approach to a patient with known or suspected cardiovascular disease begins with the time-honored traditions of a directed history and a targeted physical examination. The scope of these activities depends on the clinical context, ranging from an elective ambulatory follow-up visit to a more urgent bedside encounter. There has been a gradual decline in physical examination skills over the past few decades at every level, from student to faculty specialist, a development of great concern to both clinicians and medical educators. Classic cardiac findings are recognized by only a minority of internal medicine and family practice residents. Despite popular perceptions, clinical performance does not improve predictably with experience; instead, the acquisition of new examination skills may become more difficult for a busy individual practitioner. Less time is now devoted to mentored cardiovascular examinations during the training of students and residents. One widely recognized outcome of these trends is the progressive utilization of noninvasive imaging studies to establish the presence and

subcutaneous xanthomas, particularly along the tendon sheaths or over the extensor surfaces of the extremities. Severe hypertriglyceridemia can be associated with eruptive xanthomatosis and lipemia retinalis. Palmar crease xanthomas are specific for type III hyperlipoproteinemia. Pseudoxanthoma elasticum, a disease associated with premature atherosclerosis, is manifested by a leathery, cobblestoned appearance of the skin in the axilla and neck creases and by angioid streaks on fundoscopic examination. Extensive lentigenes have been described in a variety of development delay–cardiovascular syndromes, including Carney's syndrome, which includes multiple atrial myxomas. Cutaneous manifestations of sarcoidosis such as lupus pernio and erythema nodosum may suggest this disease as a cause of an associated dilated cardiomyopathy, especially with heart block, intraventricular conduction delay, or ventricular tachycardia.

Head and Neck Dentition and oral hygiene should be assessed in every patient both as a source of potential infection and as an index of general health. A high-arched palate is a feature of Marfan syndrome and other connective tissue disease syndromes. Bifid uvula has been described in patients with Loeys-Dietz syndrome, and orange tonsils are characteristic of Tangier disease. The ocular manifestations of hyperthyroidism have been well described. Many patients with congenital heart disease have associated hypertelorism, low-set ears, or micrognathia. Blue sclerae are a feature of osteogenesis imperfecta. An arcus senilis pattern lacks specificity as an index of coronary heart disease risk. The fundoscopic examination is an often-underused method by which to assess the microvasculature, especially among patients with established atherosclerosis, hypertension, or diabetes mellitus. A mydriatic agent may be necessary for optimal visualization. A fundoscopic examination should be performed routinely in the assessment of patients with suspected endocarditis and those with a history of acute visual change. Branch retinal artery occlusion or visualization of a Hollenhorst plaque can narrow the differential diagnosis rapidly in the appropriate setting. Relapsing polychondritis may manifest as an inflamed pinna or, in its later stages, as a saddle-nose deformity because of destruction of nasal cartilage; granulomatosis with polyangiitis can also lead to a saddle-nose deformity.

Chest Midline sternotomy, right anterior thoracotomy, left posterolateral thoracotomy, or infraclavicular scars should not be overlooked and may provide the first clue regarding an underlying cardiovascular disorder in patients unable to provide a relevant history. A prominent venous collateral pattern may suggest subclavian or vena caval obstruction. If the head and neck appear dusky and slightly cyanotic and the venous pressure is grossly elevated without visible pulsations, a diagnosis of superior vena cava syndrome should be entertained. Thoracic cage abnormalities have been well described among patients with connective tissue disease syndromes. They include pectus carinatum ("pigeon chest") and pectus excavatum ("funnel chest"). Obstructive lung disease is suggested by a barrel chest deformity, especially with tachypnea, pursed-lip breathing, and use of accessory muscles. The characteristically severe kyphosis and compensatory lumbar, pelvic, and knee flexion of ankylosing spondylitis should prompt careful auscultation for a murmur of aortic regurgitation (AR). Straight back syndrome refers to the loss of the normal kyphosis of the thoracic spine and has been described in patients with mitral valve prolapse (MVP) and its variants. In some patients with cyanotic congenital heart disease, the chest wall appears to be asymmetric, with anterior displacement of the left hemithorax. The respiratory rate and pattern should be noted during spontaneous breathing and sleep, with additional attention to depth, audible wheezing, and stridor. Lung examination can reveal adventitious sounds indicative of pulmonary edema, pneumonia, or pleuritis.

Abdomen In some patients with advanced obstructive lung disease, the point of maximal cardiac impulse may be in the epigastrium. The liver is frequently enlarged and tender in patients with chronic heart failure. Systolic pulsations over the liver signify severe tricuspid regurgitation (TR). Splenomegaly may be a feature of infective endocarditis, particularly when symptoms have persisted for weeks

or months. Ascites is a nonspecific finding but may be present with advanced chronic right heart failure, constrictive pericarditis, hepatic cirrhosis, or an intraperitoneal malignancy. The finding of an elevated JVP implies a cardiovascular etiology. In nonobese patients, the aorta typically is palpated between the epigastrium and the umbilicus. The sensitivity of palpation for the detection of an abdominal aortic aneurysm (pulsatile and expansile mass) decreases as a function of body size. Because palpation alone is not sufficiently accurate to establish this diagnosis, a screening ultrasound examination is advised when appropriate. The presence of an arterial bruit over the abdomen suggests high-grade atherosclerotic disease, although precise localization is difficult.

Extremities The temperature and color of the extremities, the presence of clubbing, arachnodactyly, and pertinent nail findings can be surmised quickly during the examination. Clubbing implies the presence of central right-to-left shunting, although it has also been described in patients with endocarditis. Its appearance can range from cyanosis and softening of the root of the nail bed, to the classic loss of the normal angle between the base of the nail and the skin, to the skeletal and periosteal bony changes of hypertrophic osteoarthropathy, which is seen rarely in patients with advanced lung or liver disease. Patients with the Holt-Oram syndrome have an unopposable, "fingerized" thumb, whereas patients with Marfan syndrome may have arachnodactyly and a positive "wrist" (overlapping of the thumb and fifth finger around the wrist) or "thumb" (protrusion of the thumb beyond the ulnar aspect of the hand when the fingers are clenched over the thumb in a fist) sign. The Janeway lesions of endocarditis are nontender, slightly raised hemorrhagic lesions on the palms and soles, whereas Osler's nodes are tender, raised nodules on the pads of the fingers or toes. Splinter hemorrhages are classically identified as linear petechiae in the midposition of the nail bed and should be distinguished from the more common traumatic petechiae, which are seen closer to the distal edge.

Lower extremity or presacral edema in the setting of an elevated JVP defines volume overload and may be a feature of chronic heart failure or constrictive pericarditis. Lower extremity edema in the absence of jugular venous hypertension may be due to profound hypoalbuminemia as seen in nephrotic syndrome or liver failure. Other causes include lymphatic or venous obstruction or, more commonly, venous insufficiency, as would be further suggested by the appearance of varicosities, venous ulcers (typically medial in location), and brownish cutaneous discoloration from hemosiderin deposition (eburnation). Pitting edema can also be seen in patients who use dihydropyridine calcium channel blockers. A Homans' sign (posterior calf pain on active dorsiflexion of the foot against resistance) is neither specific nor sensitive for deep venous thrombosis. Muscular atrophy or the absence of hair along an extremity is consistent with severe arterial insufficiency or a primary neuromuscular disorder.

■ CARDIOVASCULAR EXAMINATION

Jugular Venous Pressure and Waveform The JVP is the single most important bedside measurement from which to estimate the volume status. The internal jugular vein is preferred because the external jugular vein is valved and not directly in line with the superior vena cava and right atrium. Nevertheless, the external jugular vein has been used to discriminate between high and low central venous pressure (CVP). Precise estimation of the central venous or right atrial pressure from bedside assessment of the jugular venous waveform can be difficult. Venous pressure traditionally has been measured as the vertical distance between the top of the jugular venous pulsation and the sternal inflection point (angle of Louis). A distance >4.5 cm at 30° elevation is considered abnormal. However, the actual distance between the mid-right atrium and the angle of Louis varies considerably as a function of both body size and the patient angle at which the assessment is made (30°, 45°, or 60°). The use of the sternal angle as a reference point leads to systematic underestimation of CVP, and this method should be used less for semiquantification than to distinguish a normal from an elevated CVP. The use of the clavicle may provide an easier reference

for standardization. Venous pulsations above this level in the sitting position are clearly abnormal, as the distance between the clavicle and the right atrium is at least 10 cm. The patient should always be placed in the sitting position, with the legs dangling below the bedside, when an elevated pressure is suspected in the semisupine position. It should also be noted that bedside estimates of CVP are made in centimeters of water, and must be converted to millimeters of mercury to provide correlation with accepted hemodynamic norms ($1.36 \text{ cmH}_2\text{O} = 1.0 \text{ mmHg}$).

The venous waveform sometimes can be difficult to distinguish from the carotid pulse, especially during casual inspection. Nevertheless, the venous waveform has several characteristic features, and its individual components can be appreciated in most patients (Fig. 246-1). The arterial pulsation is not easily obliterated with palpation; the venous waveform in patients with sinus rhythm is usually biphasic, while the carotid pulse is monophasic; and the jugular venous pulsation should change with changes in posture or inspiration (unless the venous pressure is quite elevated).

The venous waveform is divided into several distinct peaks. The *a* wave reflects right atrial presystolic contraction and occurs just after the electrocardiographic P wave, preceding the first heart sound (S_1). A prominent *a* wave is seen in patients with reduced right ventricular compliance; a cannon *a* wave occurs with atrioventricular (AV) dissociation and right atrial contraction against a closed tricuspid valve. In a patient with a wide complex tachycardia, the appreciation of cannon *a* waves in the jugular venous waveform identifies the rhythm as ventricular in origin. The *a* wave is not present with atrial fibrillation. The *x* descent defines the fall in right atrial pressure after tricuspid valve opening, and occurs after inscription of the *a* wave. The *c* wave, which occurs as the closed tricuspid valve is pushed into the right atrium during early ventricular systole, interrupts this *x* descent and is followed by a further descent. The *v* wave represents atrial filling (atrial diastole) and occurs during ventricular systole. The height of the *v* wave is determined by right atrial compliance as well as the volume of blood returning to the right atrium either antegrade from the cavae or retrograde through an incompetent tricuspid valve. In patients with TR, the *v* wave is accentuated and the subsequent fall in pressure (*y* descent) is rapid. With progressive degrees of TR, the *v* wave merges with the *c* wave, and the right atrial and jugular vein waveforms become “ventricularized.” The *y* descent, which follows the peak of the *v* wave, can become prolonged or blunted with obstruction to right ventricular inflow, as may occur with tricuspid stenosis or pericardial tamponade. Normally, the venous pressure should fall by at least 3 mmHg with inspiration. Kussmaul’s sign is defined by either a rise or a lack of fall of the JVP with inspiration and is classically associated with constrictive pericarditis, although it has been reported in patients with restrictive cardiomyopathy, massive pulmonary embolism, right ventricular infarction, and advanced left ventricular (LV) systolic heart failure. It is also a common, isolated finding in patients after cardiac surgery without other hemodynamic abnormalities.

Venous hypertension sometimes can be elicited by passive leg elevation or performance of the abdominojugular reflux maneuver. When these signs are positive, a volume-overloaded state with limited compliance of an overly distended or constricted venous system is present. Abdominojugular reflux is produced with firm and consistent pressure over the upper portion of the abdomen, preferably over the right upper quadrant, for >15 s. A positive response is defined by a sustained rise of >3 cm in the JVP during the application of firm abdominal pressure. The response should be assessed after 10 s of continuous pressure to allow for respiratory artifacts and tensing of the abdominal muscles to subside. Patients must be coached to refrain from breath holding or a Valsalva-like maneuver during the procedure. Performance of the abdominojugular reflux maneuver is useful in predicting a pulmonary artery wedge pressure >15 mmHg in patients with heart failure.

Although the JVP estimates right ventricular filling pressure, it has a predictable relationship with the pulmonary artery wedge pressure. In a large study of patients with advanced heart failure, the

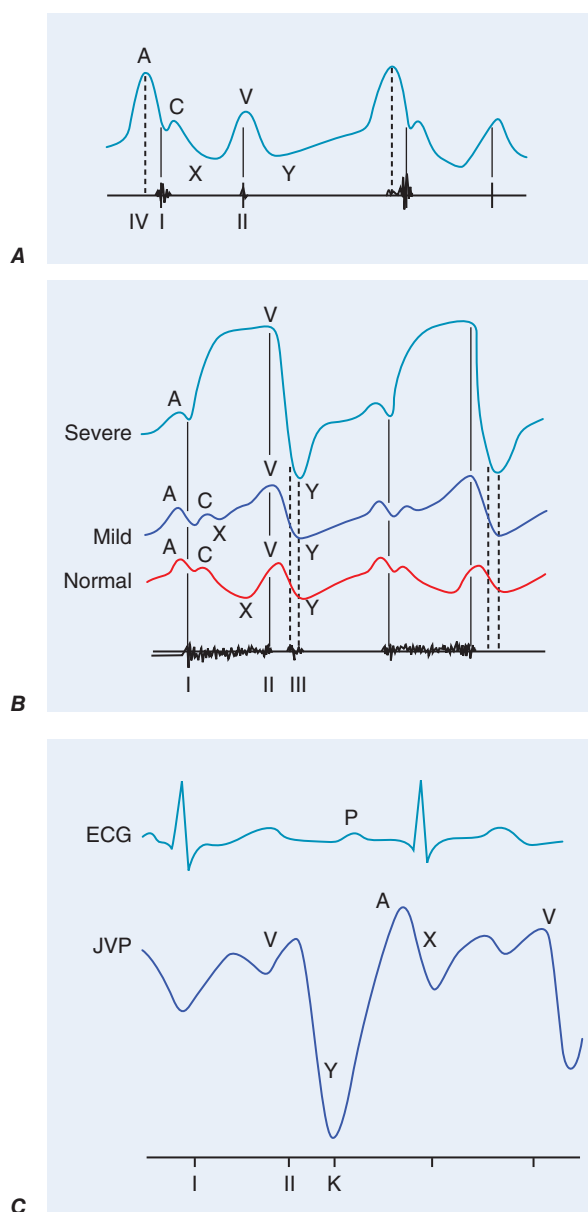


FIGURE 246-1 A. Jugular venous pulse wave tracing (top) with heart sounds (bottom) in a patient with reduced right ventricular compliance. The A wave represents right atrial presystolic contraction and occurs just after the electrocardiographic P wave and just before the first heart sound (I). In this example, the A wave is accentuated and larger than normal due to decreased right ventricular compliance, as also suggested by the right-sided S_4 (IV). The C wave may reflect the carotid pulsation in the neck and/or an early systolic increase in right atrial pressure as the right ventricle pushes the closed tricuspid valve into the right atrium. The *x* descent follows the A wave just as atrial pressure continues to fall. The V wave represents atrial filling during ventricular systole and peaks at the second heart sound (II). The *y* descent corresponds to the fall in right atrial pressure after tricuspid valve opening. B. Jugular venous wave forms in mild (middle) and severe (top) tricuspid regurgitation, compared with normal (bottom), with phonocardiographic representation of the corresponding heart sounds below. With increasing degrees of tricuspid regurgitation, the waveform becomes “ventricularized.” C. Electrocardiogram (ECG) (top), jugular venous waveform (JVP) (middle), and heart sounds (bottom) in pericardial constriction. Note the prominent and rapid *y* descent, corresponding in timing to the pericardial knock (K). (Reproduced with permission from J Abrams: *Synopsis of Cardiac Physical Diagnosis*, 2nd ed. Boston, Butterworth Heinemann, 2001.)

presence of a right atrial pressure >10 mmHg (as predicted on bedside examination) had a positive value of 88% for the prediction of a pulmonary artery wedge pressure of >22 mmHg. In addition, an elevated JVP has prognostic significance in patients with both symptomatic heart failure and asymptomatic LV systolic dysfunction. The presence of an elevated JVP is associated with a higher risk of subsequent hospitalization for heart failure, death from heart failure, or both.

Assessment of Blood Pressure Measurement of blood pressure usually is delegated to a medical assistant but should be repeated by the examining clinician. Accurate measurement depends on body position, arm size, time of measurement, place of measurement, type of device, device size, technique, and examiner. In general, physician-recorded blood pressures are higher than both nurse-recorded pressures and self-recorded pressures at home. Blood pressure is best measured in the seated position with the arm at the level of the heart and the feet on the floor with the back supported, using an appropriately sized cuff, after 5–10 min of relaxation. When it is measured in the supine position, the arm should be raised to bring it to the level of the mid-right atrium. The length and width of the blood pressure cuff bladder should be 80 and 40% of the arm's circumference, respectively. A common source of error in practice is to use an inappropriately small cuff, resulting in marked overestimation of true blood pressure, or an inappropriately large cuff, resulting in underestimation of true blood pressure. The cuff should be inflated to 30 mmHg above the expected systolic pressure and the pressure released at a rate of 2–3 mmHg/s. Systolic and diastolic pressures are defined by the first and fifth Korotkoff sounds, respectively. Very low (even 0 mmHg) diastolic blood pressures may be recorded in patients with chronic, severe AR or a large arteriovenous fistula because of enhanced diastolic “run-off.” In these instances, both the phase IV and phase V Korotkoff sounds should be recorded. Blood pressure is best assessed at the brachial artery level, though it can be measured at the radial, popliteal, or pedal artery level. In general, systolic pressure increases and diastolic pressure decreases when measured in more distal arteries. Blood pressure should be measured in both arms, and the difference should be <10 mmHg. A blood pressure differential that exceeds this threshold may be associated with atherosclerotic or inflammatory subclavian artery disease, supraaortic stenosis, aortic coarctation, or aortic dissection. Systolic leg pressures are usually as much as 20 mmHg higher than systolic arm pressures. Greater leg–arm pressure differences are seen in patients with chronic severe AR as well as patients with extensive and calcified lower extremity peripheral arterial disease. The ankle-brachial index (systolic pressure in the dorsalis pedis and/or posterior tibial artery divided by the higher of the two brachial artery pressures) is a powerful predictor of long-term cardiovascular mortality.

The blood pressure measured in an office or hospital setting may not accurately reflect the pressure in other venues. “White coat hypertension” (elevated clinic blood pressure and normal out of clinic blood pressure) is defined by at least three separate clinic-based measurements >130/80 mmHg and at least two non-clinic-based measurements <130/80 mmHg in the absence of any evidence of target organ damage. Individuals with white coat hypertension may not benefit from drug therapy, although they may be more likely to develop sustained hypertension over time. Masked hypertension (normal or low clinic blood pressure but elevated out of clinic blood pressure) should be suspected when normal or even low blood pressures are recorded in the office in patients with advanced atherosclerotic disease, especially when evidence of target organ damage is present or bruits are audible. Higher systolic blood pressures measured with a 24-h ambulatory blood pressure device are associated with a higher risk of cardiovascular disease and all-cause death independent of blood pressures measured in the outpatient setting.

Orthostatic hypotension is defined by a fall in systolic pressure >20 mmHg or in diastolic pressure >10 mmHg within 3 minutes of assumption of the upright posture from a supine position. There may also be a lack of a compensatory tachycardia, an abnormal response that suggests autonomic insufficiency, as may be seen in patients with diabetes mellitus or Parkinson's disease. Orthostatic hypotension is a common cause of postural lightheadedness/syncope and should be assessed routinely in patients for whom this diagnosis might pertain. It can be exacerbated by advanced age, dehydration, certain medications, food, deconditioning, and ambient temperature/humidity.

Arterial Pulse The carotid artery pulse occurs just after the ascending aortic pulse. The aortic pulse is best appreciated in the epigastrium, just above the level of the umbilicus. Peripheral arterial

pulses that should be assessed routinely include the subclavian, brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial. In patients in whom the diagnosis of either temporal arteritis or polymyalgia rheumatica is suspected, the temporal arteries also should be examined. Although one of the two pedal pulses may not be palpable in up to 10% of normal subjects, the pair should be symmetric. The integrity of the arcuate system of the hand is assessed by Allen's test, which is performed routinely before instrumentation of the radial artery. The pulses should be examined for their symmetry, volume, timing, contour, amplitude, and duration. If necessary, simultaneous auscultation of the heart can help identify a delay in the arrival of an arterial pulse. Simultaneous palpation of the radial and femoral pulses may reveal a femoral delay in a patient with upper extremity hypertension and suspected aortic coarctation. The carotid upstrokes should never be examined simultaneously or before listening for a bruit. Light pressure should always be used to avoid precipitation of carotid hypersensitivity syndrome and syncope in a susceptible elderly individual. The arterial pulse usually becomes more rapid and spiking as a function of its distance from the heart, a phenomenon that reflects the muscular status of the more peripheral arteries and the summation of the incident and reflected waves. In general, the character and contour of the arterial pulse depend on the stroke volume, ejection velocity, vascular compliance, and systemic vascular resistance. The pulse examination can be misleading in patients with reduced cardiac output and in those with stiffened arteries from aging, chronic hypertension, or peripheral arterial disease.

The character of the pulse is best appreciated at the carotid level (Fig. 246-2). A weak and delayed pulse (*pulsus parvus et tardus*) defines severe aortic stenosis (AS). Some patients with AS may also have a slow, notched, or interrupted upstroke (anacrotic pulse) with a thrill

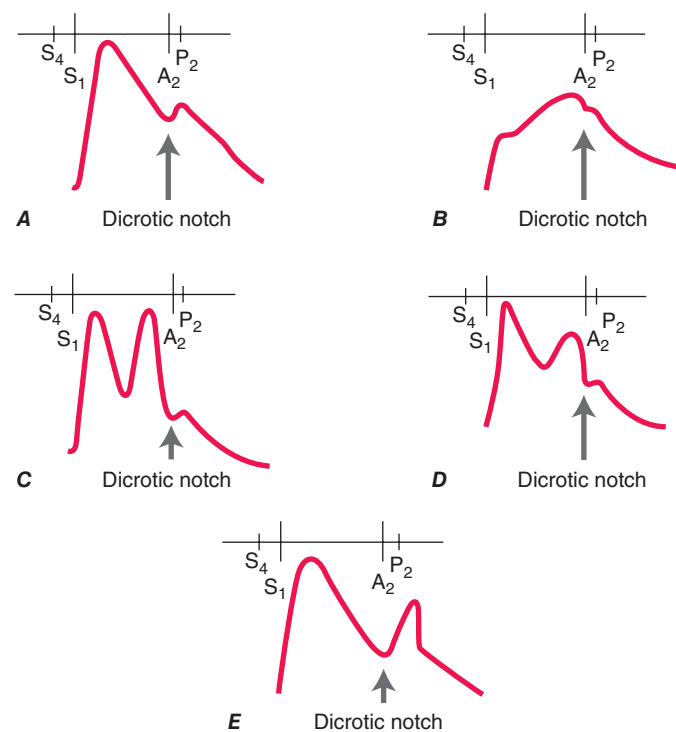


FIGURE 246-2 Schematic diagrams of the configurational changes in carotid pulse and their differential diagnoses. Heart sounds are also illustrated. **A.** Normal. S_4 , fourth heart sound; S_1 , first heart sound; A_2 , aortic component of second heart sound; P_2 , pulmonic component of second heart sound. **B.** Aortic stenosis. Anacrotic pulse with slow upstroke (tardus) to a reduced peak (parvus). **C.** Bisferiens pulse with two peaks in systole. This pulse is rarely appreciated in patients with severe aortic regurgitation. **D.** Bisferiens pulse in hypertrophic obstructive cardiomyopathy. There is a rapid upstroke to the first peak (percussion wave) and a slower rise to the second peak (tidal wave). **E.** Dicrotic pulse with peaks in systole and diastole. This waveform may be seen in patients with sepsis or during intraaortic balloon counterpulsation with inflation just after the dicrotic notch. (Reproduced with permission from K Chatterjee, W Parmley [eds]: *Cardiology: An Illustrated Text/Reference*. Philadelphia, Gower Medical Publishers, 1991.)

or shudder. With chronic severe AR, by contrast, the carotid upstroke has a sharp rise and rapid fall-off (Corrigan's or water-hammer pulse). Some patients with advanced AR may have a bifid or bisferiens pulse, in which two systolic peaks can be appreciated. A bifid pulse is also described in patients with hypertrophic obstructive cardiomyopathy (HOCM), with inscription of percussion and tidal waves. A bifid pulse is easily appreciated in patients on intraaortic balloon counterpulsation (IABP), in whom the second pulse is diastolic in timing.

Pulsus paradoxus refers to a fall in systolic pressure >10 mmHg with inspiration that is seen in patients with pericardial tamponade but also is described in those with massive pulmonary embolism, hemorrhagic shock, severe obstructive lung disease, and tension pneumothorax. Pulsus paradoxus is measured by noting the difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each heartbeat, independent of the respiratory phase. Between these two pressures, the Korotkoff sounds are heard only intermittently and during expiration. The cuff pressure must be decreased slowly to appreciate the finding. It can be difficult to measure pulsus paradoxus in patients with tachycardia, atrial fibrillation, or tachypnea. A pulsus paradoxus may be palpable at the brachial artery or femoral artery level when the pressure difference exceeds 15 mmHg. This inspiratory fall in systolic pressure is an exaggerated consequence of interventricular dependence.

Pulsus alternans, in contrast, is defined by beat-to-beat variability of pulse amplitude. It is present only when every other phase I Korotkoff sound is audible as the cuff pressure is lowered slowly, typically in a patient with a regular heart rhythm and independent of the respiratory cycle. Pulsus alternans is seen in patients with severe LV systolic

dysfunction and is thought to be due to cyclic changes in intracellular calcium and action potential duration. When pulsus alternans is associated with electrocardiographic T-wave alternans, the risk for an arrhythmic event appears to be increased.

Ascending aortic aneurysms can rarely be appreciated as a pulsatile mass in the right parasternal area. Appreciation of a prominent abdominal aortic pulse should prompt noninvasive imaging with ultrasound or computed tomography for better characterization. Femoral and/or popliteal artery aneurysms should be sought in patients with abdominal aortic aneurysm disease.

The level of a claudication-producing arterial obstruction can often be identified on physical examination (Fig. 246-3). For example, in a patient with calf claudication, a decrease in pulse amplitude between the common femoral and popliteal arteries will localize the obstruction to the level of the superficial femoral artery, although inflow obstruction above the level of the common femoral artery may coexist. Auscultation for carotid, subclavian, abdominal aortic, and femoral artery bruits should be routine. However, the correlation between the presence of a bruit and the degree of vascular obstruction is poor. A cervical bruit is a weak indicator of the degree of carotid artery stenosis; the absence of a bruit does not exclude the presence of significant luminal obstruction. If a bruit extends into diastole or if a thrill is present, the obstruction is usually severe. Another cause of an arterial bruit is an arteriovenous fistula with enhanced flow.

The likelihood of significant lower extremity peripheral arterial disease increases with typical symptoms of claudication, cool skin, abnormalities on pulse examination, or the presence of a vascular bruit. Abnormal pulse oximetry (a >2% difference between finger and toe oxygen saturation) can be used to detect lower extremity peripheral

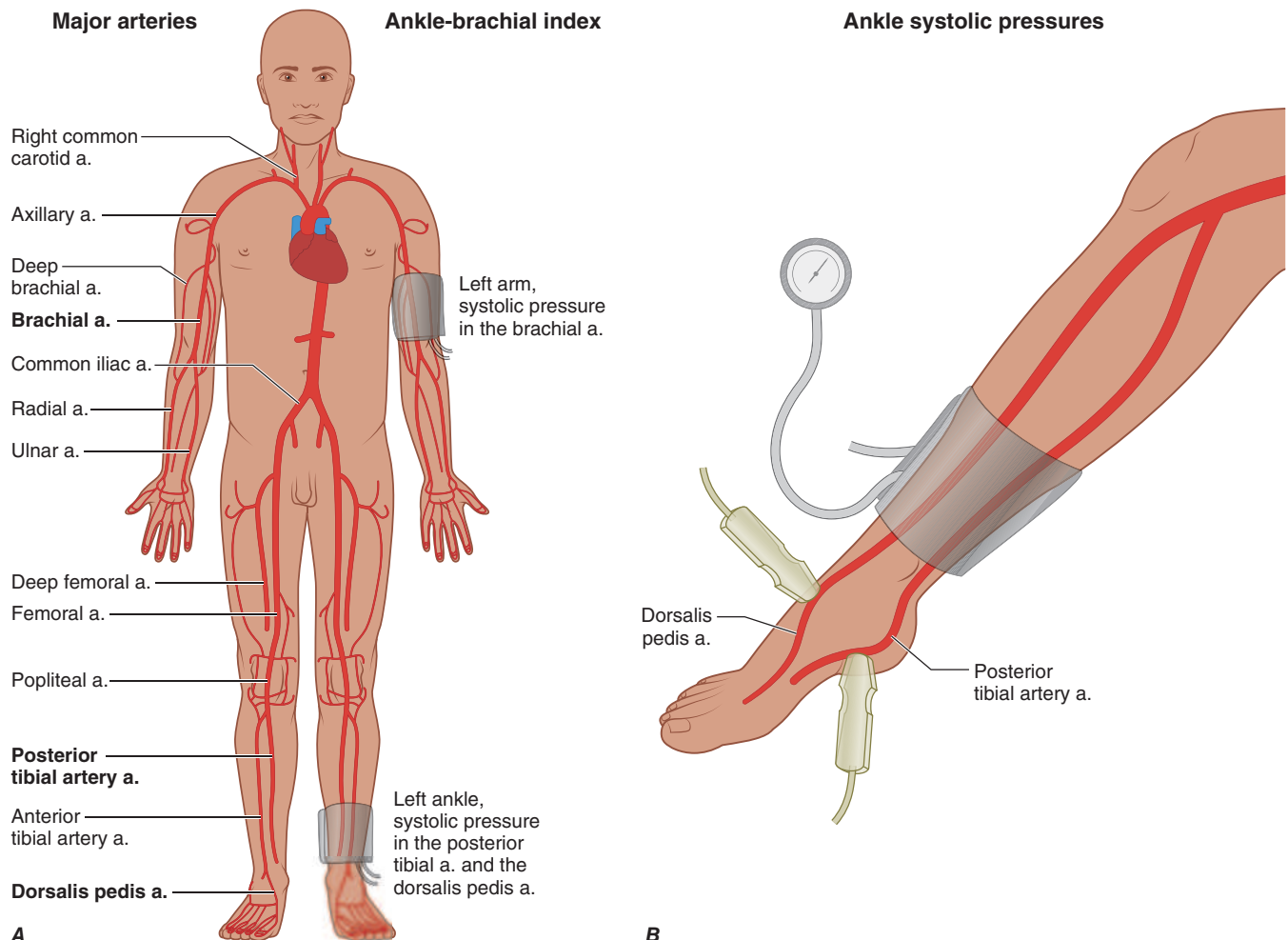


FIGURE 246-3 **A.** Anatomy of the major arteries of the leg. **B.** Measurement of the ankle systolic pressure. The ankle-brachial index (ABI) is calculated by dividing the lower of the two ankle pressures (i.e., the dorsalis pedis or posterior tibia) by the higher of the two arm pressures (i.e., left or right arm). Left and right ABIs should be recorded. (Adapted from NA Khan et al: Does the clinical examination predict lower extremity peripheral arterial disease? JAMA 295:536, 2006.)

Inspection and Palpation of the Heart The LV apex beat may be visible in the midclavicular line at the fifth intercostal space in thin-chested adults. Visible pulsations anywhere other than this expected location are abnormal. The left anterior chest wall may heave in patients with an enlarged or hyperdynamic left or right ventricle. As noted previously, a visible right upper parasternal pulsation may be suggestive of ascending aortic aneurysm disease. In thin, tall patients and patients with advanced obstructive lung disease and flattened diaphragms, the cardiac impulse may be visible in the epigastrium and should be distinguished from a pulsatile liver edge.

Palpation of the heart begins with the patient in the supine position at 30° and can be enhanced by placing the patient in the left lateral decubitus position. The normal LV impulse is <2 cm in diameter and moves quickly away from the fingers; it is better appreciated at end expiration, with the heart closer to the anterior chest wall. Characteristics such as size, amplitude, and rate of force development should be noted.

Enlargement of the LV cavity is manifested by a leftward and downward displacement of an enlarged apex beat. A sustained apex beat is a sign of pressure overload, such as that which may be present in patients with AS or chronic hypertension. A palpable presystolic impulse corresponds to the fourth heart sound (S_4) and is indicative of reduced LV compliance and the forceful contribution of atrial contraction to ventricular filling. A palpable third sound (S_3), which is indicative of a rapid early filling wave in patients with heart failure, may be present even when the gallop itself is not audible. A large LV aneurysm may sometimes be palpable as an ectopic impulse, discrete from the apex beat and often dyskinetic. HOCM may very rarely cause a triple cadence beat at the apex with contributions from a palpable S_4 and the two components of the bisferiens systolic pulse.

Right ventricular pressure or volume overload may create a sternal lift. Signs of either TR (*cv* waves in the jugular venous pulse) and/or pulmonary arterial hypertension (a loud single or palpable P_2) would be confirmatory. The right ventricle can enlarge to the extent that left-sided events are obscured. A zone of retraction between the right ventricular and LV impulses sometimes can be appreciated in patients with right ventricle pressure or volume overload when they are placed in the left lateral decubitus position. Systolic and diastolic thrills signify turbulent and high-velocity blood flow. Their locations help identify the origin of heart murmurs.

CARDIAC AUSCULTATION

Heart Sounds Ventricular systole is defined by the interval between the first (S_1) and second (S_2) heart sounds (Fig. 246-4). The first heart sound (S_1) includes mitral and tricuspid valve closure. Normal splitting can be appreciated in young patients and those with right bundle branch block, in whom tricuspid valve closure is relatively delayed. The intensity of S_1 is determined by the distance over which the anterior leaflet of the mitral valve must travel to return to its annular plane, leaflet mobility, LV contractility, and the PR interval. S_1 is classically loud in the early phases of rheumatic MS and in patients with hyperkinetic circulatory states or short PR intervals. S_1 becomes softer in the later stages of MS when the leaflets are rigid and calcified, after exposure to β -adrenergic receptor blockers, with long PR intervals, and with LV contractile dysfunction. The intensity of heart sounds, however, can be reduced by any process that increases the distance between the stethoscope and the responsible cardiac event, including mechanical ventilation, obstructive lung disease, obesity, pneumothorax, and a pericardial effusion.

Aortic and pulmonic valve closure constitutes the second heart sound (S_2). With normal or physiologic splitting, the A_2 - P_2 interval increases with inspiration and narrows during expiration. This physiologic interval will widen with right bundle branch block because of the further delay in pulmonic valve closure and in patients with severe MR because of the premature closure of the aortic valve. An unusually

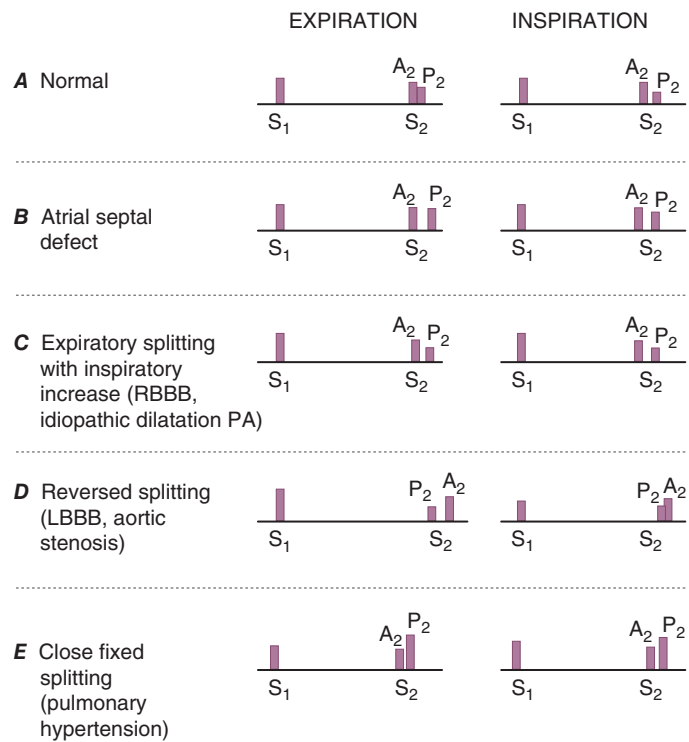


FIGURE 246-4 Heart sounds. A. Normal. S_1 , first heart sound; S_2 , second heart sound; A_2 , aortic component of the second heart sound; P_2 , pulmonic component of the second heart sound. B. Atrial septal defect with fixed splitting of S_2 . C. Physiologic but wide splitting of S_2 with right bundle branch block (RBBB). PA, pulmonary artery. D. Reversed or paradoxical splitting of S_2 with left bundle branch block (LBBB). E. Narrow splitting of S_2 with pulmonary hypertension. (Reproduced with permission from NO Fowler: *Diagnosis of Heart Disease*, Springer Nature; 1991.)

narrowly split or even a singular S_2 is a feature of pulmonary arterial hypertension. Fixed splitting of S_2 , in which the A_2 - P_2 interval is wide and does not change during the respiratory cycle, occurs in patients with a secundum atrial septal defect (ASD). Reversed or paradoxical splitting refers to a pathologic delay in aortic valve closure, such as that which occurs in patients with left bundle branch block, right ventricular pacing, severe AS, HOCM, and acute myocardial ischemia. With reversed or paradoxical splitting, the individual components of S_2 are audible at end expiration, and their interval narrows with inspiration, the opposite of what would be expected under normal physiologic conditions. P_2 is considered loud when its intensity exceeds that of A_2 at the base, when it can be palpated in the area of the proximal main pulmonary artery (second left interspace), or when both components of S_2 can be appreciated at the lower left sternal border or apex. The intensity of A_2 and P_2 decreases with AS and pulmonic stenosis (PS), respectively. In these conditions, a single S_2 may result.

Systolic Sounds An ejection sound is a high-pitched early systolic sound that corresponds in timing to the upstroke of the carotid pulse. It usually is associated with congenital bicuspid aortic or pulmonic valve disease; however, ejection sounds are also sometimes audible in patients with isolated aortic or pulmonary root dilation and normal semilunar valves. The ejection sound that accompanies bicuspid aortic valve disease becomes softer and then inaudible as the valve calcifies and becomes more rigid. The ejection sound that accompanies PS moves closer to the first heart sound as the severity of the stenosis increases. In addition, the pulmonic ejection sound is the only right-sided acoustic event that *decreases* in intensity with inspiration. Ejection sounds are often heard more easily at the lower left sternal border than they are at the base. Nonejection sounds (clicks), which occur after the onset of the carotid upstroke, are related to MVP and may be single or multiple. The nonejection click may introduce a murmur. This click-murmur complex will move away from the first heart sound with maneuvers that increase ventricular preload, such as squatting. On standing, the click and murmur move closer to S_1 .

Diastolic Sounds The high-pitched opening snap (OS) of MS occurs after a very short interval after the second heart sound. The A_2 -OS interval is inversely proportional to the height of the left atrial-left ventricular diastolic pressure gradient. The intensity of both S_1 and the OS of MS decreases with progressive calcification and rigidity of the anterior mitral leaflets. The pericardial knock (PK) is also high-pitched and occurs slightly later than the OS, corresponding in timing to the abrupt cessation of ventricular expansion after tricuspid valve opening and to an exaggerated y descent seen in the jugular venous waveform in patients with constrictive pericarditis. A tumor plop is a lower-pitched sound that rarely can be heard in patients with atrial myxoma. It may be appreciated only in certain positions and arises from the diastolic prolapse of the tumor across the mitral valve.

The third heart sound (S_3) occurs during the rapid filling phase of ventricular diastole. It can be a normal finding in children, adolescents, and young adults; however, in older patients, it signifies heart failure. A left-sided S_3 is a low-pitched sound best heard over the LV apex. A right-sided S_3 is usually better heard over the lower left sternal border and becomes louder with inspiration. A left-sided S_3 in patients with chronic heart failure is predictive of cardiovascular morbidity and mortality. Interestingly, an S_3 is equally prevalent among heart failure patients with preserved and reduced LV ejection fraction.

The fourth heart sound (S_4) occurs during the atrial filling phase of ventricular diastole and indicates LV presystolic expansion. An S_4 is more common among patients who derive significant benefit from the atrial contribution to ventricular filling, such as those with chronic LV hypertrophy or active myocardial ischemia. An S_4 is not present with atrial fibrillation.

Cardiac Murmurs Heart murmurs result from audible vibrations that are caused by increased turbulence and are defined by their timing within the cardiac cycle. Not all murmurs are indicative of structural heart disease, and the accurate identification of a benign or functional systolic murmur often can obviate the need for additional testing in healthy subjects, especially children and adolescents. The duration, frequency, configuration, and intensity of a heart murmur are dictated by the magnitude, variability, and duration of the responsible pressure difference between two cardiac chambers, the two ventricles, or the ventricles and their respective great arteries. The intensity of a heart murmur is graded on a scale of 1 to 6; a thrill is present with murmurs of grade 4 or greater intensity. Other attributes of the murmur that aid in its accurate identification include its location, radiation, and response to bedside maneuvers. Although clinicians can detect and correctly identify heart murmurs with only fair reliability, a careful and complete bedside examination usually can identify individuals with valvular heart disease for whom transthoracic echocardiography and clinical follow-up are indicated and exclude subjects for whom no further evaluation is necessary.

Systolic murmurs can be early, mid, late, or holosystolic in timing (Fig. 246-5). Acute severe MR results in a decrescendo early systolic murmur, the characteristics of which are related to the progressive attenuation of the LV to left atrial pressure gradient during systole because of the steep and rapid rise in left atrial pressure in this context. Severe MR associated with posterior leaflet prolapse or flail radiates anteriorly and to the base, where it can be confused with the murmur of AS. MR that is due to anterior leaflet involvement radiates posteriorly and to the axilla. With acute TR in patients with normal pulmonary artery pressures, an early systolic murmur that may increase in intensity with inspiration may be heard at the left lower sternal border, with regurgitant cv waves visible in the jugular venous pulse.

A midsystolic murmur begins after S_1 and ends before S_2 ; it is typically crescendo-decrescendo in configuration. AS is the most common cause of a midsystolic murmur in an adult. It is often difficult to estimate the severity of the valve lesion on the basis of the physical examination findings, especially in older hypertensive patients with stiffened carotid arteries or patients with low cardiac output in whom the intensity of the systolic heart murmur is misleadingly soft. Examination findings consistent with severe AS would include *parvus et tardus* carotid upstrokes, a late-peaking grade 3 or greater

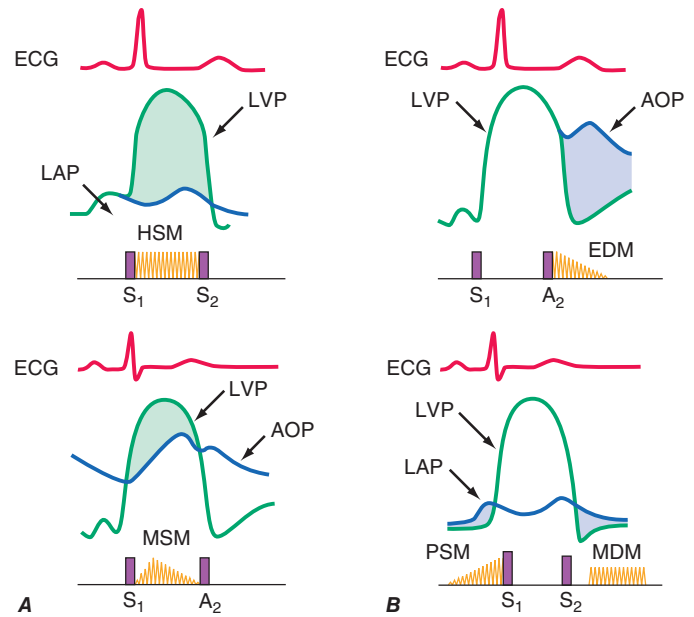


FIGURE 246-5 **A. Top.** Graphic representation of the systolic pressure difference (green shaded area) between left ventricle and left atrium with phonocardiographic recording of a holosystolic murmur (HSM) indicative of mitral regurgitation. ECG, electrocardiogram; LAP, left atrial pressure; LVP, left ventricular pressure; S_1 , first heart sound; S_2 , second heart sound. **Bottom.** Graphic representation of the systolic pressure gradient (green shaded area) between left ventricle and aorta in patient with aortic stenosis. A midsystolic murmur (MSM) with a crescendo-decrescendo configuration is recorded. AOP, aortic pressure. **B. Top.** Graphic representation of the diastolic pressure difference between the aorta and left ventricle (blue shaded area) in a patient with aortic regurgitation, resulting in a decrescendo, early diastolic murmur (EDM) beginning with A_2 . **Bottom.** Graphic representation of the diastolic left atrial-left ventricular gradient (blue areas) in a patient with mitral stenosis with a mid-diastolic murmur (MDM) and late presystolic murmurs (PSM).

midsystolic murmur, a soft A_2 , a sustained LV apical impulse, and an S_4 . It is sometimes difficult to distinguish aortic sclerosis from more advanced degrees of valve stenosis. The former is defined by focal thickening and calcification of the aortic valve leaflets that is not severe enough to result in obstruction. These valve changes are associated with a Doppler jet velocity across the aortic valve of 2.5 m/s or less. Patients with aortic sclerosis can have grade 2 or 3 midsystolic murmurs identical in their acoustic characteristics to the murmurs heard in patients with more advanced degrees of AS. Other causes of a midsystolic heart murmur include pulmonic valve stenosis (with or without an ejection sound), HOCM, increased pulmonary blood flow in patients with a large ASD and left-to-right shunting, and several states associated with accelerated blood flow in the absence of structural heart disease, such as fever, thyrotoxicosis, pregnancy, anemia, and normal childhood/adolescence.

The murmur of HOCM has features of both obstruction to LV outflow and MR, as would be expected from knowledge of the pathophysiology of this condition. The systolic murmur of HOCM usually can be distinguished from other causes on the basis of its response to bedside maneuvers, including Valsalva, passive leg raising, and standing/squatting. In general, maneuvers that decrease LV preload (or increase LV contractility) will cause the murmur to intensify, whereas maneuvers that increase LV preload or afterload will cause a decrease in the intensity of the murmur. Accordingly, the systolic murmur of HOCM becomes louder during the strain phase of the Valsalva maneuver and after standing quickly from a squatting position. The murmur becomes softer with passive leg raising and when squatting. The murmur of AS is typically loudest in the second right interspace with radiation into the carotids, whereas the murmur of HOCM is best heard between the lower left sternal border and the apex. The murmur of PS is best heard in the second left interspace. The midsystolic murmur associated with enhanced pulmonic blood flow in the setting of a large ASD is usually loudest at the mid-left sternal border.

A late systolic murmur, heard best at the apex, indicates MVP. As previously noted, the murmur may or may not be introduced by one or more nonejection clicks. Differential radiation of the murmur, as previously described, may help identify the specific leaflet involved by the myxomatous process. The click-murmur complex behaves in a manner directionally similar to that demonstrated by the murmur of HOCM during the Valsalva and stand/squat maneuvers (Fig. 246-6). The murmur of MVP can be identified by the accompanying nonejection click.

Holosystolic murmurs are plateau in configuration and reflect a continuous and wide pressure gradient between the left ventricle and left atrium with chronic MR, the left ventricle and right ventricle with a ventricular septal defect (VSD), and the right ventricle and right atrium with TR. In contrast to acute MR, in chronic MR, the left atrium is enlarged and its compliance is normal or increased to the extent that there is little if any further increase in left atrial pressure from any increase in regurgitant volume. The murmur of MR is best heard over the cardiac apex. The intensity of the murmur increases with maneuvers that increase LV afterload, such as sustained hand grip. The murmur of a VSD (without significant pulmonary hypertension) is holosystolic and loudest at the mid-left sternal border, where a thrill is usually present. The murmur of TR is loudest at the lower left sternal border, increases in intensity with inspiration (Carvallo's sign), and is accompanied by visible *cv* waves in the jugular venous wave form and, on occasion, by pulsatile hepatomegaly.

Diastolic Murmurs In contrast to some systolic murmurs, diastolic heart murmurs always signify structural heart disease (Fig. 246-5). The murmur associated with acute, severe AR is relatively soft and of short duration because of the rapid rise in LV diastolic pressure and the progressive diminution of the aortic-LV diastolic pressure gradient. In contrast, the murmur of chronic severe AR is classically heard as a decrescendo, blowing diastolic murmur along the left sternal border in patients with primary valve pathology and sometimes along the right sternal border in patients with primary aortic root pathology. When the jet of AR is directed posteriorly along the anterior leaflet of the mitral valve, the intensity of the murmur may be attenuated, and severity of the valve lesion underestimated. Detection of subtle AR murmurs can be enhanced by auscultation and end-expiration with the patient leaning forward. With chronic, severe AR, the pulse pressure is wide and the arterial pulses are bounding in character. Signs of significant diastolic run-off are often absent in the acute phase. The murmur of pulmonic regurgitation is also heard along the left sternal border. It is most commonly due to pulmonary hypertension and enlargement of the annulus of the pulmonic valve. S_2 is single and loud and may be palpable. There is a right ventricular/parasternal lift that is indicative of chronic right ventricular pressure overload. A less impressive murmur of PR is present after repair of tetralogy of Fallot or pulmonic valve atresia. In this postoperative setting, the murmur is softer and lower-pitched, and the severity of the accompanying pulmonic regurgitation can be underestimated significantly.

MS is the classic cause of a mid- to late-diastolic murmur, which is best heard over the apex in the left lateral decubitus position, is low-pitched or rumbling, and is introduced by an OS in the early stages of the rheumatic disease process. Presystolic accentuation refers to an increase in the intensity of the murmur just before the first heart sound and occurs in patients with sinus rhythm. It is absent in patients with atrial fibrillation. The auscultatory findings in patients with rheumatic

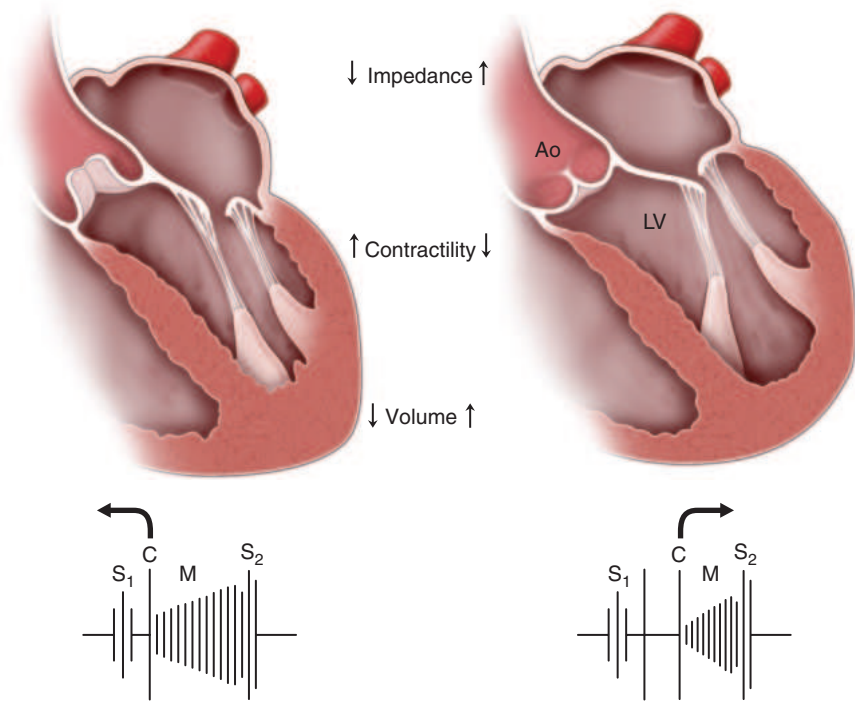


FIGURE 246-6 Behavior of the click (C) and murmur (M) of mitral valve prolapse with changes in loading (volume, impedance) and contractility. S_1 , first heart sound; S_2 , second heart sound. With standing (left side of figure), volume and impedance decrease, as a result of which the click and murmur move closer to S_1 . With squatting (right), the click and murmur move away from S_1 due to the increases in left ventricular volume and impedance (afterload). Ao, aorta; LV, left ventricle. (Adapted from RA O'Rourke, MH Crawford: *Curr Prob Cardiol* 1:9, 1976.)

tricuspid stenosis typically are obscured by left-sided events, although they are similar in nature to those described in patients with MS. "Functional" mitral or tricuspid stenosis refers to the generation of mid-diastolic murmurs that are created by increased and accelerated transvalvular diastolic flow, even in the absence of valvular obstruction, in the setting of severe MR, severe TR, or a large ASD with left-to-right shunting. The Austin Flint murmur of chronic severe AR is a low-pitched mid- to late apical diastolic murmur that sometimes can be confused with MS. The Austin Flint murmur typically decreases in intensity after exposure to vasodilators, whereas the murmur of MS may be accompanied by an OS and also may increase in intensity after vasodilators because of the associated increase in cardiac output. Unusual causes of a mid-diastolic murmur include atrial myxoma, complete heart block, and acute rheumatic mitral valvulitis.

Continuous Murmur A continuous murmur is predicated on a pressure gradient that persists between two cardiac chambers or blood vessels across systole and diastole. The murmurs typically begin in systole, envelop the second heart sound (S_2), and continue through some portion of diastole. They can often be difficult to distinguish from individual systolic and diastolic murmurs in patients with mixed valvular heart disease. The classic example of a continuous murmur is that associated with a PDA, which usually is heard in the second or third interspace at a slight distance from the sternal border. Other causes of a continuous murmur include a ruptured sinus of Valsalva aneurysm with creation of an aortic-right atrial or right ventricular fistula, a coronary or great vessel arteriovenous fistula, and an arteriovenous fistula constructed to provide dialysis access. There are two types of benign continuous murmurs. The cervical venous hum is heard in children or adolescents in the supraclavicular fossa. It can be obliterated with firm pressure applied to the diaphragm of the stethoscope, especially when the subject turns their head toward the examiner. The mammary soufflé of pregnancy relates to enhanced arterial blood flow through engorged breasts. The diastolic component of the murmur can be obliterated with firm pressure over the stethoscope.

TABLE 246-1 Effects of Physiologic Interventions on the Intensity of Heart Murmurs and Sounds**Respiration**

Right-sided murmurs and sounds generally increase with inspiration, except for the PES. Left-sided murmurs and sounds are usually louder during expiration.

Valsalva Maneuver

Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HOCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. After release of the Valsalva maneuver, right-sided murmurs tend to return to control intensity earlier than do left-sided murmurs.

After VPB or AF

Murmurs originating at normal or stenotic semilunar valves increase in the cardiac cycle after a VPB or in the cycle after a long cycle length in AF. By contrast, systolic murmurs due to AV valve regurgitation do not change or become shorter (MVP).

Positional Changes

With *standing*, most murmurs diminish, with two exceptions being the murmur of HOCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With *squatting*, most murmurs become louder, but those of HOCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results.

Exercise

Murmurs due to blood flow across normal or obstructed valves (e.g., PS, MS) become louder with both isotonic and submaximal isometric (hand grip) exercise. Murmurs of MR, VSD, and AR also increase with hand grip exercise. However, the murmur of HOCM often decreases with nearly maximum hand grip exercise. Left-sided S_4 and S_3 sounds are often accentuated by exercise, particularly when due to ischemic heart disease.

Abbreviations: AF, atrial fibrillation; AR, aortic regurgitation; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PES, pulmonic ejection sound; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VPB, ventricular premature beat; VSD, ventricular septal defect.

Dynamic Auscultation Diagnostic accuracy can be enhanced by the performance of simple bedside maneuvers to identify heart murmurs and characterize their significance (Table 246-1). Except for the pulmonic ejection sound, right-sided events increase in intensity with inspiration and decrease with expiration; left-sided events behave oppositely (100% sensitivity, 88% specificity). As previously noted, the intensity of the murmurs associated with MR, VSD, and AR will increase in response to maneuvers that increase LV afterload, such as hand grip and vasopressors. The intensity of these murmurs will decrease after exposure to vasodilating agents. Squatting is associated with an abrupt increase in LV preload and afterload, whereas rapid standing results in a sudden decrease in preload. In patients with MVP, the click and murmur move away from the first heart sound with squatting because of the delay in onset of leaflet prolapse at higher ventricular volumes. With rapid standing, however, the click and murmur move closer to the first heart sound as prolapse occurs earlier in systole at a smaller chamber dimension. The murmur of HOCM behaves similarly, becoming softer and shorter with squatting (95% sensitivity, 85% specificity) and longer and louder on rapid standing (95% sensitivity, 84% specificity). A change in the intensity of a systolic murmur in the first beat after a premature beat or in the beat after a long cycle length in patients with atrial fibrillation suggests valvular AS rather than MR, particularly in an older patient in whom the murmur of the AS may be well transmitted to the apex (Gallavardin effect). Of note, however, the systolic murmur of HOCM also increases in intensity in the beat after a premature beat. This increase in intensity of any LV outflow murmur in the beat after a premature beat relates to the combined effects of enhanced LV filling (from the longer diastolic period) and postextrasystolic potentiation of LV contractile function. In either instance, forward flow will accelerate, causing an increase in the gradient across the LV outflow tract (dynamic or fixed) and a louder systolic murmur. In contrast, the intensity of the murmur of MR does not change in a postpremature beat, because there is relatively little change in the nearly constant LV to left atrial pressure gradient or

further alteration in mitral valve flow. Bedside exercise can sometimes be performed to increase cardiac output and, secondarily, the intensity of both systolic and diastolic heart murmurs. Most left-sided heart murmurs decrease in intensity and duration during the strain phase of the Valsalva maneuver. The murmurs associated with MVP and HOCM are the two notable exceptions. The Valsalva maneuver also can be used to assess the integrity of the heart and vasculature in the setting of advanced heart failure.

Prosthetic Heart Valves The first clue that prosthetic valve dysfunction may contribute to recurrent symptoms is frequently a change in the quality of the heart sounds or the appearance of a new murmur. The heart sounds with a bioprosthetic valve resemble those generated by native valves. A mitral bioprosthesis usually may be associated with a grade 1 to 2 midsystolic murmur along the left sternal border (created by turbulence across the valve struts as they project into the LV outflow tract) as well as by a soft mid-diastolic murmur that occurs with normal LV filling. This diastolic murmur often can be heard only in the left lateral decubitus position and after exercise. A high-pitched or holosystolic apical murmur is indicative of pathologic MR due to a paravalvular leak and/or intra-annular bioprosthetic regurgitation from leaflet degeneration, for which diagnostic noninvasive imaging is indicated. Clinical deterioration can occur rapidly after the first expression of mitral bioprosthetic valve failure. A tissue valve in the aortic position is always associated with a grade 1 to 3 midsystolic murmur at the base or just below the suprasternal notch. A diastolic murmur of AR is abnormal in any circumstance. Mechanical valve dysfunction may first be suggested by a decrease in the intensity of either the opening or the closing sound. A high-pitched apical systolic murmur in patients with a mechanical mitral prosthesis and a diastolic decrescendo murmur in patients with a mechanical aortic prosthesis indicate paravalvular regurgitation. Patients with prosthetic valve thrombosis may present clinically with signs of shock, muffled heart sounds, and soft murmurs in both systole and diastole.

Pericardial Disease A pericardial friction rub is nearly 100% specific for the diagnosis of acute pericarditis, although the sensitivity of this finding is not nearly as high, because the rub may come and go over the course of an acute illness or be very difficult to elicit. The rub is heard as a leathery or scratchy three-component or two-component sound, although it may be monophasic. Classically, the three components are ventricular systole, rapid early diastolic filling, and late presystolic filling after atrial contraction in patients in sinus rhythm. It is necessary to listen to the heart in several positions. Additional clues to the presence of acute pericarditis may be present from the history and 12-lead electrocardiogram. The rub typically disappears as the volume of any pericardial effusion increases. Pericardial tamponade can be diagnosed with a sensitivity of 98%, a specificity of 83%, and a positive likelihood ratio of 5.9 (95% confidence interval 2.4–14) by a pulsus paradoxus that exceeds 12 mmHg in a patient with a large pericardial effusion.

The findings on physical examination are integrated with the symptoms previously elicited with a careful history to construct an appropriate differential diagnosis and proceed with indicated imaging and laboratory assessment. The physical examination is an irreplaceable component of clinician-patient interaction. Educational efforts to enhance competence may result in improved diagnostic efficiency. The adjunctive use of point-of-care ultrasound and artificial intelligence tools is expected to increase.

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247 Electrocardiography

Ary L. Goldberger

An *electrocardiogram* (ECG or EKG) is a graphical representation of electrical activity generated by the heart. The signals, detected by means of metallic electrodes attached to the extremities and chest wall, are amplified and recorded by the *electrocardiograph* device. ECG leads are configured to display the instantaneous *differences* in electrical potentials between specific sets of electrodes. The utility of the ECG derives from its immediate availability as a noninvasive, inexpensive, and highly versatile test. In addition to its use in detecting arrhythmias, conduction disturbances, and myocardial ischemia/infarction, the ECG may reveal findings related to life-threatening metabolic disturbances, drug toxicities, and increased susceptibility to sudden cardiac arrest (see also Chaps. 317 and 420). The importance of electrocardiologic abnormalities in the diagnosis, prognosis, and management of muscular dystrophies and other hereditary neuromuscular diseases is discussed separately (see Chap. 360).

ELECTROPHYSIOLOGIC BACKGROUND

Depolarization of the heart is the initiating event for cardiac contraction. The electrical currents that spread through the heart are produced by three components: cardiac pacemaker cells, specialized conduction tissue, and the heart muscle itself. The ECG records only the depolarization (stimulation) and repolarization (recovery) electrical activity generated by the “working” atrial and ventricular myocardium (see also Chaps. 251 and 253).

The stimulus initiating the normal heartbeat originates in the *sinoatrial* (SA) node (Fig. 247-1), which possesses spontaneous automaticity. Spread of the depolarization wave through the right and left atria induces contraction of these chambers. Next, the impulse

stimulates specialized conduction tissues in the atrioventricular (AV) nodal and His-bundle areas; together, these two regions constitute the AV junction. The bundle of His bifurcates into two main divisions, the right and left bundle branches, which rapidly transmit depolarization wavefronts in a synchronous way to the right and left ventricular myocardium via the Purkinje fibers. The main left bundle fans out into left anterior and left posterior fascicular subdivisions. The depolarization wavefronts then spread through the ventricular wall, from endocardium to epicardium, triggering coordinated ventricular contraction. Since the cardiac depolarization and repolarization wavefronts have direction and magnitude, they can be represented by vectors.

BASIC ECG WAVEFORMS AND INTERVALS

The ECG waveforms are labeled alphabetically, beginning with the P wave, which represents atrial depolarization (Fig. 247-2). The QRS complex represents ventricular depolarization; the ST-T-U complex (ST segment, T wave, and U wave) represents ventricular repolarization. The J point is the junction between the end of the QRS complex and the beginning of the ST segment. Atrial repolarization waveforms (ST-T_a) are usually too low in amplitude to be detected, but they may become apparent in acute pericarditis, atrial infarction, and AV heart block syndromes.

The QRS-T waveforms of the surface ECG correspond to sequential phases of simultaneously obtained ventricular *action potentials*, the intracellular recordings from single myocardial fibers (Chap. 251). The rapid upstroke (phase 0) of the action potential corresponds to the onset of QRS. The plateau (phase 2) corresponds to the isoelectric ST segment, and active repolarization (phase 3) corresponds to the inscription of the T wave. Factors that decrease the slope of phase 0 by impairing the influx of Na⁺ (e.g., hyperkalemia and drugs such as flecainide) tend to increase QRS duration. Factors that prolong phase 2 or 3 (e.g., amiodarone, hypocalcemia) increase the QT interval. In contrast, factors (e.g., hypercalcemia, digoxin) associated with shortening of ventricular repolarization duration abbreviate the QT. The hereditary short QT syndrome and its relationship to sudden cardiac arrest are discussed in Chap. 262.

The ECG is usually recorded on graph paper divided into a grid of 1-mm² boxes. When the recording (sweep) speed is 25 mm/s, the smallest (1 mm) horizontal divisions correspond to 40 ms (0.04 s), with heavier lines at intervals of 200 ms (0.20 s). Vertically, the ECG graph measures the amplitude of a specific wave or deflection (1 mV = 10 mm with standard calibration; the voltage criteria for hypertrophy mentioned below are given in millimeters). There are four major sets of ECG intervals: RR, PR, QRS, and QT/QT_c (Fig. 247-2). The instantaneous heart rate (beats per minute) can be computed from the inter-beat (RR) interval by dividing the number of large (0.20 s) time units

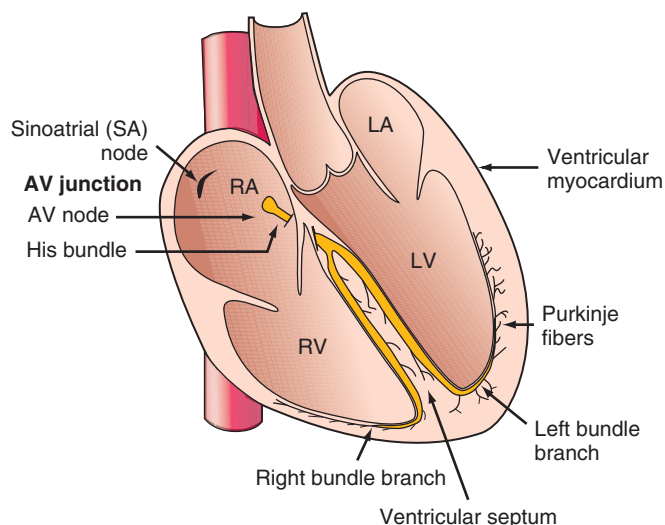


FIGURE 247-1 Schematic of the cardiac conduction system. AV, atrioventricular; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

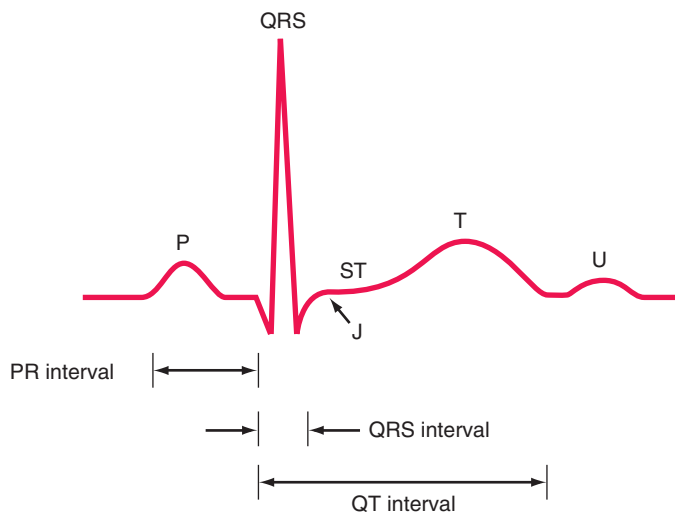


FIGURE 247-2 Basic ECG waveforms and intervals. Not shown is the RR interval, the time between consecutive QRS complexes.

between consecutive R waves into 300 or the number of small (40 ms) segments into 1500. The PR interval measures the time (normally 120–200 ms) between atrial and ventricular depolarization, which includes the physiologic delay imposed by stimulation of cells in the AV junction area. The QRS interval (normally 100–110 ms or less) reflects the duration of ventricular depolarization. The QT interval subtends both ventricular depolarization and (primarily) repolarization times and varies inversely with the heart rate. A variety of formulas has been proposed for computing a rate-corrected QT interval, termed QT_c , but without formal consensus. The classic “square root” formula ($QT_c = QT/\sqrt{RR}$, computed in second units) has been criticized for systematic errors at both lower and higher heart rates. One alternative is the Framingham formula (given here for units of milliseconds): $QT_c = QT + 0.154(1000 - RR)$. The following upper normal limits (based visually on the longest QT) have been proposed: QT_c of 460 ms in women and 450 ms in men. Lower limits are less well defined. Visual or electronic QT/QT_c measurements should be assessed in light of inherent limitations in their precise determination from standard ECGs waveforms.

ECG LEADS

The 12 conventional ECG leads are divided into two groups: six limb (extremity) leads and six chest (precordial) leads. The limb leads record potentials transmitted onto the *frontal plane* (Fig. 247-3A); the chest leads record potentials transmitted onto the *horizontal plane* (Fig. 247-3B).

The orientation and polarity of the frontal plane leads are represented on a hexaxial diagram (Fig. 247-4). The six chest leads are obtained by exploring electrodes as shown in Fig. 247-5.

Each lead is analogous to a different video camera angle “looking” at the same events—atrial and ventricular depolarization and repolarization—from different spatial orientations. The 12-lead ECG can be supplemented with additional leads in special circumstances. For example, right precordial leads V_3R to V_6R are useful in detecting evidence of acute right ventricular ischemia/infarction. Bedside monitors and ambulatory ECGs (e.g., Holter monitors, event recorders, patch electrode and other medical wearable devices) usually employ

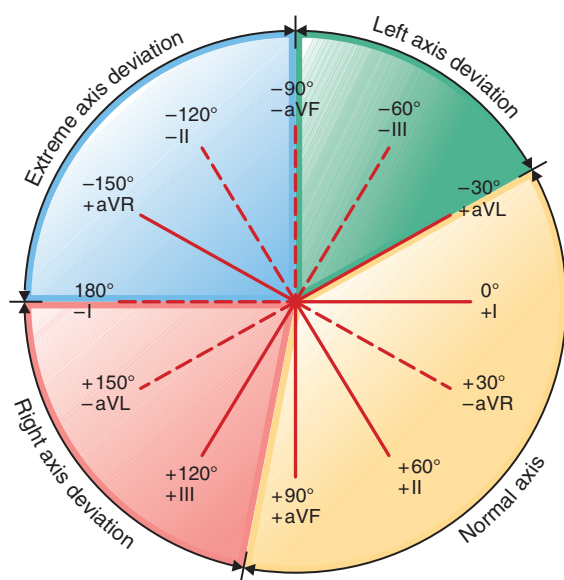


FIGURE 247-4 The frontal plane (limb or extremity) leads are represented on a hexaxial diagram. Each ECG lead has a specific spatial orientation and polarity. The positive pole of each lead axis (solid line) and the negative pole (hatched line) are designated by their angular position relative to the positive pole of lead I (0°). The mean electrical axis of the QRS complex is measured with respect to this display.

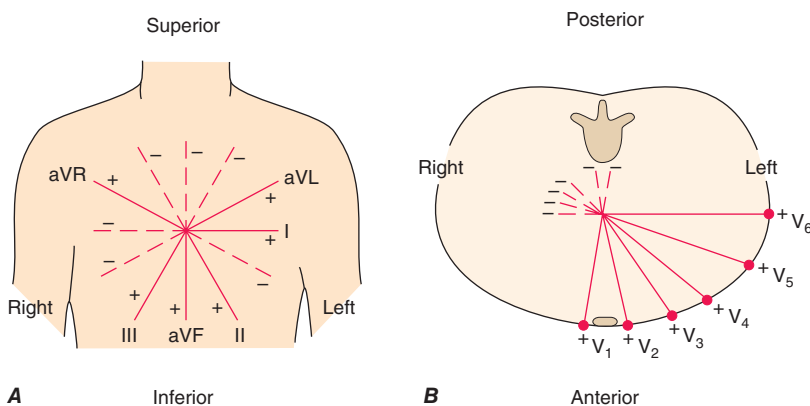


FIGURE 247-3 The six frontal plane (A) and six horizontal plane (B) leads provide a three-dimensional representation of cardiac electrical activity.

only one or two modified leads. The standard ECG leads are configured such that a positive (upright) deflection is recorded in a lead if a wave of depolarization spreads toward the positive pole of that lead, and a negative deflection is recorded if the wave spreads toward the negative pole. If the *mean* orientation of the depolarization vector is at right angles to a particular lead axis, a biphasic (equally positive and negative) deflection will be inscribed.

GENESIS OF THE NORMAL ECG

P WAVE

The normal atrial depolarization vector is oriented downward and toward the subject's left, reflecting the spread of depolarization from the sinus node to the right and then the left atrial myocardium. Since this vector points toward the positive pole of lead II and toward the negative pole of lead aVR, the sinus-generated P wave will be positive in lead II and negative in aVR. By contrast, activation of the atria from an ectopic pacemaker in the lower part of either atrium or in the AV junction region may produce retrograde P waves (negative in II, positive in aVR). The normal P wave in lead V_1 may be biphasic with a positive component reflecting right atrial depolarization, followed by a small (<1 mm²) negative component reflecting left atrial depolarization.

QRS COMPLEX

Normal ventricular depolarization proceeds as a rapid, continuous spread of activation wave fronts. This complex process can be divided

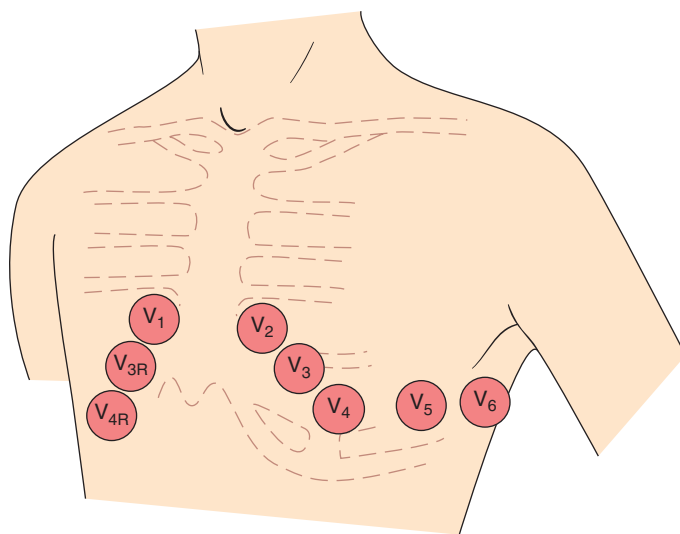


FIGURE 247-5 The horizontal plane (chest or precordial) leads are obtained with electrodes in the locations shown. Additional posterior leads are sometimes placed on the same horizontal plane as V_4 to facilitate detection of acute posterolateral infarction (V_7 , midaxillary line; V_8 , posterior axillary line; and V_9 , posterior scapular line). Right chest leads (V_3R – V_6R) may enhance detection of right ventricular involvement in the context of inferior infarction.

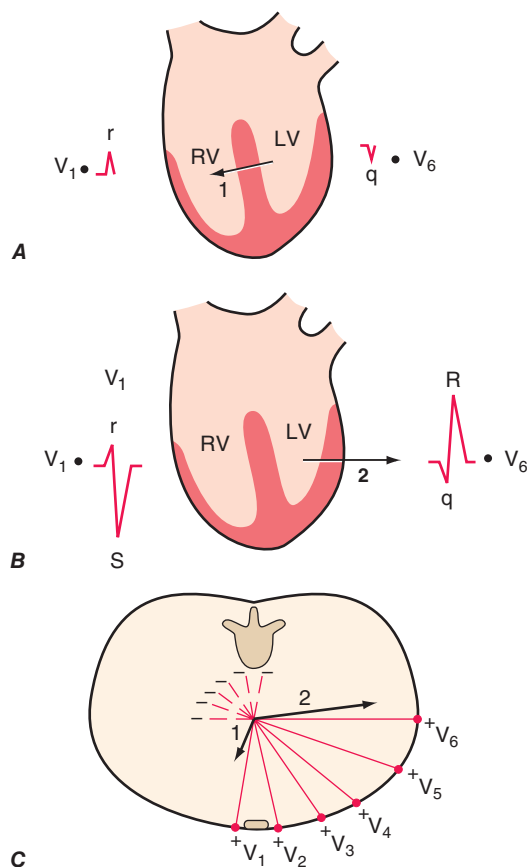


FIGURE 247-6 Ventricular depolarization can be divided into two major phases, each represented by a vector. **A.** The first phase (arrow 1) denotes depolarization of the ventricular septum, beginning on the left side and spreading to the right. This process is represented by a small “septal” r wave in lead V_1 and a small septal q wave in lead V_6 . **B.** Simultaneous depolarization of the left and right ventricles (LV and RV) constitutes the second phase. Vector 2 is oriented to the left and posteriorly, reflecting the electrical predominance of the LV. **C.** Vectors (arrows) representing these two phases are shown in reference to the horizontal plane leads. (Reproduced with permission from AL Goldberger et al: *Goldberger’s Clinical Electrocardiography: A Simplified Approach*, 10th ed. Philadelphia, Elsevier, 2024.)

into two major sequential phases, and each can be represented by a mean vector (Fig. 247-6). The first and shortest phase is depolarization of the interventricular septum, proceeding from the left to the right and anteriorly (vector 1). The second and major phase results from the simultaneous depolarization of the right and left ventricles (vector 2). This phase is normally dominated by the more massive left ventricle, so that vector 2 points leftward and posteriorly. Therefore, a right precordial lead (V_1) will record this biphasic depolarization process with a small positive deflection (septal r wave) followed by a larger negative deflection (S wave). A left precordial lead, for example, V_6 , will record the same sequence with a small negative deflection (septal q wave) followed by a relatively tall positive deflection (R wave). Intermediate leads show a relative increase in R-wave amplitude (normal R-wave progression) and a decrease in S-wave amplitude progressing across the chest from right to left. The lead where the R and S waves are of about equal amplitude is referred to as the *transition zone* (usually V_3 or V_4) (Fig. 247-7).

The QRS pattern in the extremity leads may vary considerably from one normal subject to another depending on the *electrical axis* of the QRS, which describes the mean orientation of the QRS vector with reference to the six frontal plane leads. Normally, the QRS axis ranges from -30° to $+100^\circ$ (Fig. 247-4). An axis more negative than -30° is referred to as *left axis deviation*, and an axis more positive than $+90^\circ$ to $+100^\circ$ is referred to as *right axis deviation*. Left axis deviation may occur as a normal variant but is more commonly associated with left ventricular hypertrophy, a block in the anterior fascicle of the left bundle system (left anterior fascicular block or hemiblock), or inferior myocardial infarction. Right axis deviation also may occur as a normal variant (particularly in children and young adults), as a spurious finding due to reversal of the left and right arm electrodes, or in conditions such as right ventricular overload (acute or chronic), lateral infarction, dextrocardia, left pneumothorax, and left posterior fascicular block.

■ T WAVE AND U WAVE

Normally, the mean T-wave vector is oriented roughly concordant with the mean QRS vector (within about 45° in the frontal plane). Since depolarization and repolarization are electrically opposite processes, this normal QRS-T-wave vector concordance indicates that repolarization normally must proceed in the reverse direction from depolarization (i.e., from ventricular epicardium to endocardium). The normal U wave is a small, rounded deflection (≤ 1 mm) that follows the T wave and usually has the same polarity as the T wave. An abnormal increase in U-wave amplitude is most commonly due to hypokalemia or drugs (e.g., dofetilide, amiodarone, sotalol, quinidine). Very prominent U waves, as part of prolonged ventricular repolarization syndromes, are a marker of increased susceptibility to *torsades de pointes* (Chap. 253).

MAJOR ECG ABNORMALITIES

■ CARDIAC ENLARGEMENT AND HYPERTROPHY

Right atrial overload (acute or chronic) may lead to an increase in P-wave amplitude (≥ 2.5 mm) (Fig. 247-8), previously referred to as “P-pulmonale.” Left atrial overload typically produces a biphasic P wave in V_1 with a broad negative component or a broad (≥ 120 ms), often with a notched P wave in one or more limb leads (Fig. 247-8). This pattern, historically referred to as “P-mitrale,” may occur with *interatrial conduction delays* in the absence of actual atrial enlargement, leading to the more general designation of *left atrial abnormality*.

Right ventricular hypertrophy due to a sustained, severe pressure load (e.g., with pulmonic valve stenosis or certain pulmonary artery hypertension syndromes) is characterized by a relatively tall R wave in lead V_1 ($R \geq S$ wave), usually with right axis deviation (Fig. 247-9); alternatively, there may be a qR pattern in V_1 or V_3R . ST depression and T-wave inversion in the right to mid-precordial leads are also

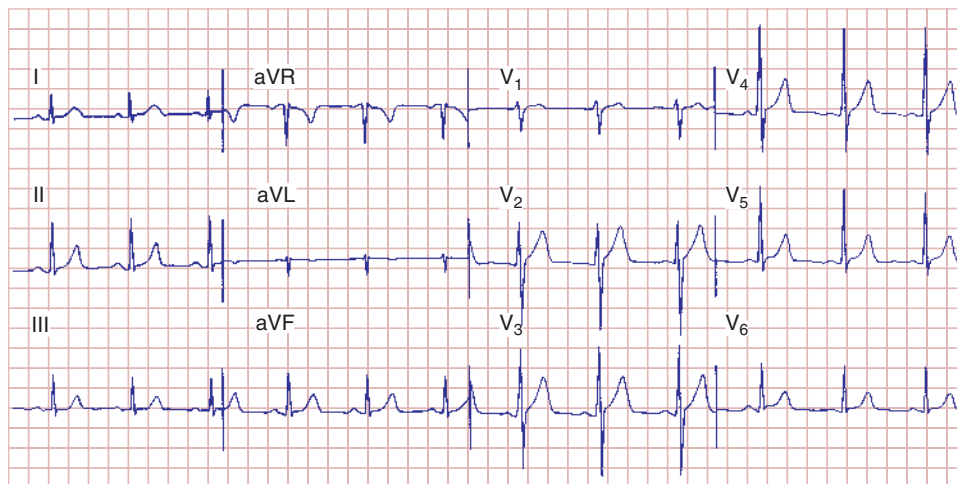


FIGURE 247-7 Normal electrocardiogram from a healthy male subject. Sinus rhythm is present with a heart rate of 75 beats per minute. PR interval is 160 ms; QRS interval (duration) is 80 ms; QT interval is 360 s; QT_c (Framingham formula) is about 390 ms; the mean QRS axis is about $+70^\circ$. The precordial leads show normal R-wave progression with the transition zone (R wave $\approx$ S wave) in lead V_3 .

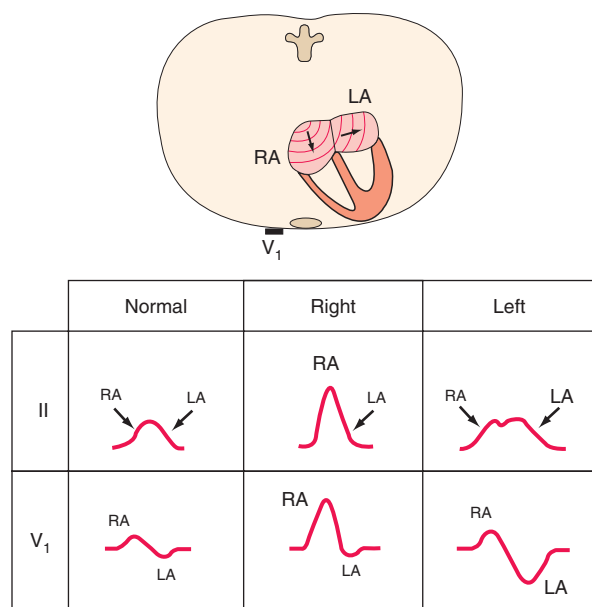


FIGURE 247-8 Right atrial (RA) overload may cause tall, peaked P waves in the limb or precordial leads. Left atrial (LA) abnormality may cause broad, often notched P waves in the limb leads and a biphasic P wave in lead V₁ with a prominent negative component representing delayed depolarization of the LA. (Reproduced with permission from MK Park, WG Guntheroth: *How to Read Pediatric ECGs*, 4th ed. St. Louis, Mosby/Elsevier, 2006.)

often present. This pattern, formerly called right ventricular “strain,” is attributable to repolarization abnormalities in acutely or chronically overloaded muscle. Prominent S waves may occur in the left lateral precordial leads. Right ventricular hypertrophy due to ostium secundum atrial septal defects, with the accompanying right ventricular volume overload, is commonly associated with an incomplete or complete right bundle branch block pattern in concert with a rightward QRS axis.

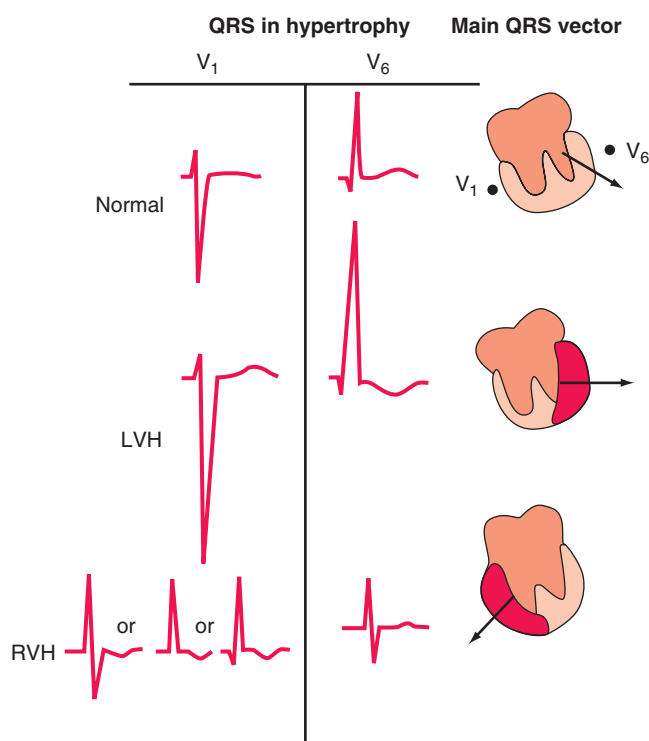


FIGURE 247-9 Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qR complex in lead V₁. T-wave inversions may be present in right precordial leads.

Acute cor pulmonale due to pulmonary thromboembolism (Chap. 290) or acute respiratory distress syndromes (e.g., COVID-19) may be associated with a normal ECG or a variety of abnormalities. Sinus tachycardia is the most common arrhythmia, although other tachyarrhythmias, such as atrial fibrillation or flutter, may occur. The QRS axis may shift to the right, sometimes in concert with the so-called S₁Q₃T₃ pattern (prominence of the S wave in lead I and the Q wave in lead III, with T-wave inversion in lead III). Acute right ventricular dilation also may be associated with slow R-wave progression and ST-T abnormalities in V₁ to V₄ simulating acute anterior infarction. A right ventricular conduction disturbance may appear.

Chronic cor pulmonale due to obstructive lung disease (Chap. 307) usually does not produce the classic ECG patterns of right ventricular hypertrophy noted above. Instead of tall right precordial R waves, emphysema is more typically associated with diminished r waves in right to mid-precordial leads (slow R-wave progression) due in part to downward displacement of the diaphragm and the heart. Low-voltage complexes are commonly present, owing to hyperaeration.

Multiple voltage criteria for *left ventricular hypertrophy* (Fig. 247-9) have been proposed based on the presence of tall left precordial R waves and deep right precordial S waves (e.g., SV₁ + [RV₅ or RV₆] >35 mm). Repolarization abnormalities (ST depression with T-wave inversions, formerly called the left ventricular “strain” pattern) may appear in leads with prominent R waves. However, prominent precordial voltages occur as a common normal variant, especially in athletic or young individuals. Left ventricular hypertrophy may increase limb lead voltage with or without increased precordial voltage (e.g., RaVL + SV₅ >20 mm in women and >28 mm in men). The presence of left atrial abnormality increases the likelihood of underlying left ventricular hypertrophy in cases with borderline voltage criteria. Left ventricular hypertrophy often progresses to incomplete or complete left bundle branch block. The sensitivities of conventional voltage criteria for left ventricular hypertrophy are low in middle age to older adults and may be decreased further in obese persons and smokers, as well as with right bundle branch block. ECG evidence for left ventricular hypertrophy is a major noninvasive marker of increased risk of cardiovascular morbidity and mortality rates, including sudden cardiac death. However, because of false-positive and false-negative diagnoses, the ECG is of limited utility in diagnosing atrial or ventricular enlargement. More definitive anatomic and functional information is provided by echocardiographic and cardiac magnetic resonance imaging studies (Chaps. 248 and A9).

■ BUNDLE BRANCH BLOCKS AND RELATED PATTERNS

Intrinsic impairment of conduction in either the right or the left bundle system (intraventricular conduction disturbances) leads to prolongation of the QRS interval. With complete bundle branch blocks, the widest QRS interval is ≥120 ms in duration; with incomplete blocks, the QRS interval is between about 110 and 120 ms. The QRS vector usually is oriented in the direction of the myocardial region where depolarization is delayed (Fig. 247-10). Thus, with right bundle branch block, the terminal QRS vector is oriented to the right and anteriorly (rSR' in V₁ and qRS in V₆, typically). Left bundle branch block alters both early and later phases of ventricular depolarization. The major QRS vector is directed to the left and posteriorly. In addition, the normal early left-to-right pattern of septal activation is disrupted such that septal depolarization proceeds from right to left as well. As a result, left bundle branch block generates wide, predominantly negative (QS) complexes in lead V₁ and entirely positive (R) complexes in V₆. Waveform patterns identical to those of left bundle branch block, preceded by a sharp (sometimes very low amplitude) spike, are seen in most cases of electronic right ventricular pacing due to the relative delay in left ventricular activation.

Bundle branch block may occur in a variety of conditions. In subjects without structural heart disease, right bundle branch block is seen more commonly than left bundle branch block. Right bundle branch block also occurs with heart disease, both congenital (e.g., atrial septal defect) and acquired (e.g., valvular, ischemic). Left bundle branch block is often a marker of one of four underlying conditions associated with increased risk of cardiovascular morbidity and mortality rates: coronary

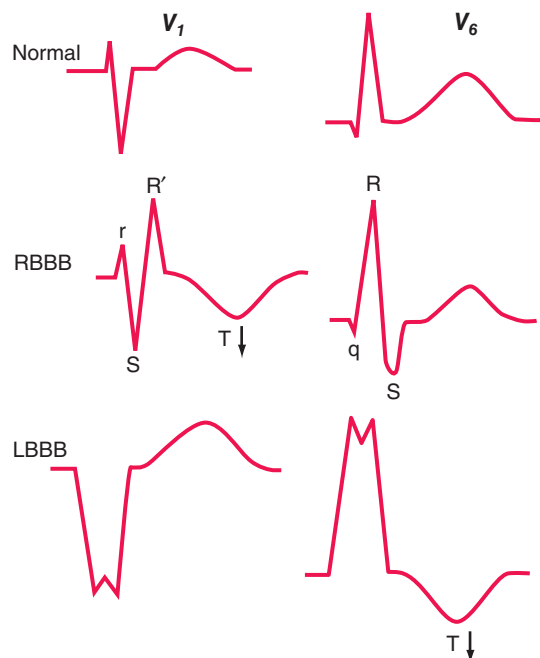


FIGURE 247-10 Comparison of typical QRS-T patterns in right bundle branch block (RBBB) and left bundle branch block (LBBB) with the normal pattern in leads V_1 and V_6 . Note the secondary T-wave inversions (arrows) in leads with an rSR' complex with RBBB and in leads with a wide R wave with LBBB.

heart disease (frequently with impaired left ventricular function), hypertensive heart disease, aortic valve disease (including after transcatheter aortic valve replacement), and cardiomyopathy. Bundle branch blocks may be chronic or intermittent. A bundle branch block may be rate-related, most commonly observed when the heart rate exceeds some critical value.

Bundle branch blocks and depolarization abnormalities secondary to artificial pacemakers not only affect ventricular depolarization (QRS) but also are characteristically associated with *secondary repolarization* (ST-T) abnormalities. With bundle branch blocks, the T wave is typically opposite in polarity to the last deflection of the QRS (Fig. 247-10). This discordance of the QRS-T-wave vectors is caused by the altered sequence of repolarization that occurs as a consequence of altered depolarization. In contrast, *primary repolarization* abnormalities are independent of QRS changes and are related instead to actual alterations in the electrical properties of the myocardial fibers themselves (e.g., in the resting membrane potential or action potential duration), not just to changes in the sequence of repolarization. Ischemia, electrolyte imbalance, and drugs such as digoxin all cause such primary ST-T-wave changes. Primary and secondary T-wave changes may coexist. For example, T-wave inversions in the right precordial leads with left bundle branch block or in the left precordial leads with right bundle branch block may be important markers of underlying ischemia or other abnormalities. A distinctive abnormality simulating right bundle branch block with ST-segment elevations in the right chest leads is seen with the Brugada pattern (Chap. 262).

Partial blocks in the left bundle system (left anterior or posterior fascicular blocks; formerly called hemiblocks) generally do not prolong

the QRS duration substantially. Instead, they are associated with shifts in the frontal plane QRS axis (leftward or rightward, respectively). Left anterior fascicular block (QRS axis more negative than -45°) is probably the most common cause of marked left axis deviation in adults. In contrast, left posterior fascicular block (QRS axis more rightward than $+110$ – 120°) is extremely rare as an isolated finding and requires exclusion of other factors causing right axis deviation. Intraventricular conduction delays also can be caused by factors extrinsic (toxic) to the conduction system that slow ventricular conduction, particularly hyperkalemia or drugs (e.g., class 1 antiarrhythmic agents, tricyclic antidepressants, phenothiazines). Prolongation of QRS duration does not necessarily indicate a conduction delay but may be due to *preexcitation* of the ventricles via a bypass tract, as in Wolff-Parkinson-White (WPW) patterns (Chap. 256) and related variants.

■ MYOCARDIAL ISCHEMIA AND INFARCTION

(See also Chap. 286) The ECG is central to the diagnosis of acute and chronic ischemic heart disease. Ischemia exerts complex time-dependent effects on the electrical properties of myocardial cells. Severe, acute ischemia lowers the resting membrane potential and shortens the duration of the action potential. Such changes cause a voltage gradient between normal and ischemic zones. As a consequence, current flows between those regions. These *currents of injury* are represented on the surface ECG by deviation of the ST segment (Fig. 247-11). When the acute ischemia is *transmural*, the ST vector usually is shifted in the direction of the outer (epicardial) layers, producing ST elevations and sometimes, in the earliest stages of ischemia, tall, positive so-called hyperacute T waves over the ischemic zone. With ischemia confined primarily to the *subendocardium*, the ST vector typically shifts toward the subendocardium and ventricular cavity, so that overlying (e.g., anterior precordial) leads show ST-segment depression (with ST elevation in lead aVR). Multiple factors affect the amplitude of acute ischemic ST deviations. Profound ST elevation or depression in multiple leads usually indicates very severe ischemia. The division of acute myocardial infarction due to obstructive coronary artery disease into ST-segment elevation and non-ST elevation types is useful since the consistent efficacy of emergency (minutes to hours) reperfusion therapy is limited to the former group. Indications for acute reperfusion therapy in non-ST elevation myocardial infarction are a focus of ongoing investigation (Chap. 285). Takotsubo syndrome, as well as other causes of myocardial infarction without atherosclerotic coronary disease, can simulate the patterns of acute or evolving ST-segment elevation or non-ST-segment elevation infarction (Chap. 285).

The ECG leads are usually more helpful in localizing regions of ST elevation than non-ST elevation ischemia. For example, acute transmural anterior (including apical and lateral) wall ischemia is reflected by ST elevations or increased T-wave positivity in one or more of the precordial leads (V_1 – V_6) and leads I and aVL. Inferior wall ischemia produces changes in leads II, III, and aVF. “Posterior” wall ischemia (almost always associated with lateral or inferior involvement) may be indirectly recognized by *reciprocal* ST depressions in leads V_1 to V_3 (thus constituting an ST elevation “equivalent” acute coronary syndrome). Acute right ventricular ischemia usually produces ST elevations in right-sided chest leads (Fig. 247-5). When ischemic ST elevations occur as the earliest sign of acute infarction, they typically are followed within a period ranging from hours to days by evolving T-wave inversions and often by Q waves occurring in the same lead distribution. Reversible transmural

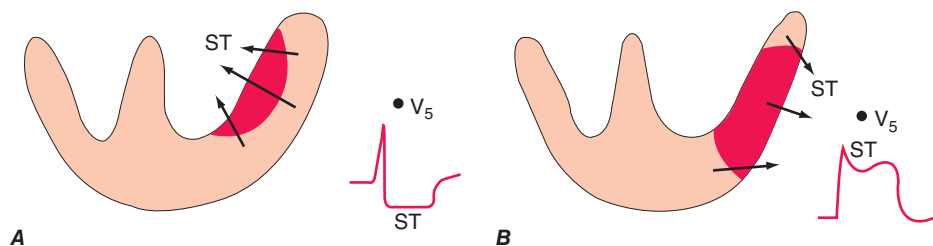


FIGURE 247-11 Acute ischemia causes a current of injury. **A.** With predominant subendocardial ischemia, the resultant ST vector will be directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore will record ST depression. **B.** With ischemia involving the outer ventricular layer (transmural or epicardial injury), the ST vector will be directed outward. Overlying leads will record ST elevation.

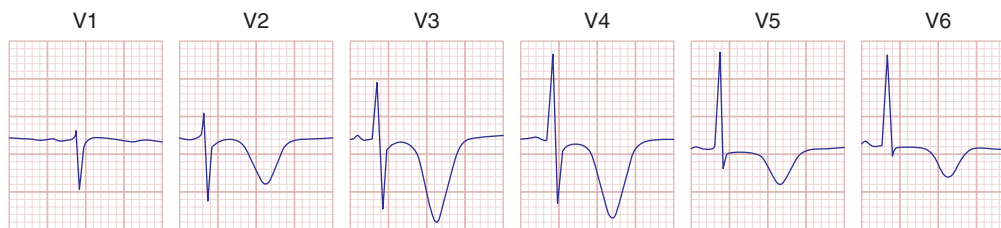


FIGURE 247-12 Severe anterior wall ischemia (with or without infarction) may cause prominent T-wave inversions in the precordial leads and in leads I and aVL. This pattern (sometimes referred to as the Wellens T wave sign) is usually associated with a high-grade stenosis of the left anterior descending coronary artery.

ischemia, for example, due to coronary vasospasm (Prinzmetal's angina) may cause transient ST-segment elevations without development of Q waves. Depending on the severity and duration of ischemia, ischemic ST elevations may resolve completely in minutes or be followed by T-wave inversions that persist for hours or even days. Patients with ischemic chest pain who present with deep T-wave inversions in multiple precordial leads (e.g., V_1 – V_4 , and sometimes I and aVL) with or without cardiac enzyme elevations typically have severe obstruction in the left anterior descending coronary artery (**Fig. 247-12**).

With infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities. Necrosis of sufficient myocardial tissue may lead to decreased R-wave amplitude or abnormal Q waves (even in the absence of transmural ischemia) in the anterior or inferior leads (**Fig. 247-13**). Abnormal Q waves were once considered markers of transmural myocardial infarction, whereas subendocardial infarcts were thought not to produce Q waves. However, transmural infarcts may occur without Q waves, and subendocardial (nontransmural) infarcts may be associated with Q waves. Therefore, evolving or chronic infarcts are more appropriately classified as “Q-wave” or “non-Q-wave” (**Chap. A7**). Loss of depolarization forces due to posterior or lateral infarction may cause reciprocal increases in R-wave amplitude in leads V_1 and V_2 without diagnostic Q waves in any of the conventional leads. (Additional leads V_7 – V_9 may show acute changes.) In the weeks and months after infarction, these ECG changes may persist or begin to resolve. Complete normalization of the ECG after Q-wave infarction is uncommon but may occur, particularly with smaller infarcts. In contrast, ST-segment elevations that persist for several weeks or more after a Q-wave infarct usually correlate with a severe underlying wall motion disorder, although not necessarily a frank ventricular aneurysm.

The ECG has important limitations in both sensitivity and specificity in the diagnosis of acute and chronic ischemic heart disease. Although a single normal ECG does not exclude ischemia or even acute infarction, a normal ECG *throughout* the course of an acute infarct is distinctly uncommon. Prolonged chest pain without diagnostic ECG changes therefore should always prompt a careful search for other non-coronary causes of chest pain (**Chap. 15**). Furthermore, the diagnostic changes of acute or evolving ischemia are often masked by the presence of left bundle branch block, electronic ventricular pacemaker patterns, and WPW preexcitation. However, clinicians may also overdiagnose ischemia or infarction based on the presence of ST-segment elevations or depressions; T-wave inversions; tall, positive T waves; or Q waves *not* related to ischemic heart disease (*pseudoinfarct* patterns). For example, ST-segment elevations simulating acute ischemia/infarction may occur with acute pericarditis or myocarditis, including COVID-19 infections, as a normal variant (including the typical “early repolarization” pattern), or in a variety of other conditions (**Table 247-1**). Similarly, tall T waves do not invariably represent hyperacute ischemic changes but may also be caused by normal variants, hyperkalemia, or cerebrovascular injury, among other causes.

ST-segment elevations and tall, positive T waves are common findings in leads V_1 and V_2 in left bundle branch block or left ventricular hypertrophy in the absence of ischemia. The differential diagnosis of Q waves includes physiologic or positional variants, ventricular hypertrophy, acute or chronic noncoronary myocardial injury, hypertrophic cardiomyopathy, and ventricular conduction disorders. Ventricular hypertrophy, hypokalemia, drugs such as digoxin, and a variety of other factors may cause ST-segment depression mimicking subendocardial ischemia. Prominent T-wave inversion may occur with

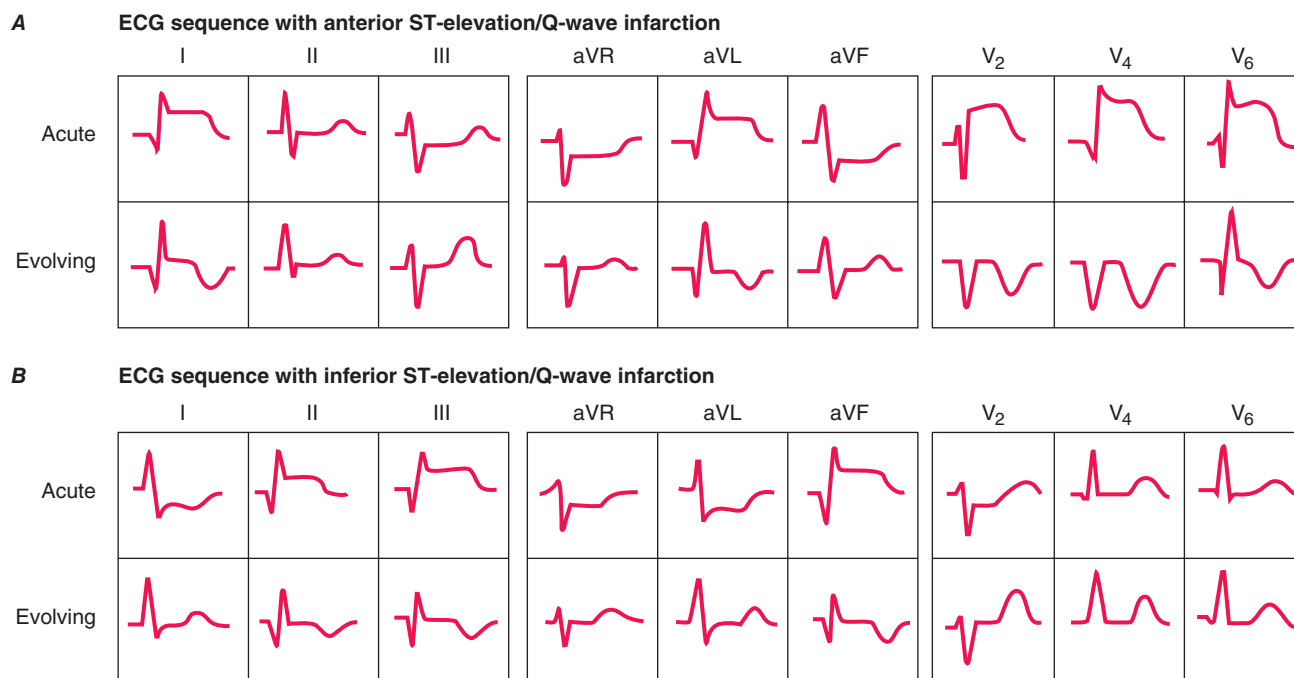


FIGURE 247-13 Sequence of depolarization and repolarization changes with acute and evolving anterior (A) and (B) inferior ST-elevation/Q-wave infarctions. With anterior infarcts, ST elevation in leads I and aVL and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or posterolateral) infarcts may be associated with reciprocal ST depressions in leads V_1 to V_3 . (Reproduced with permission from AL Goldberger et al: *Goldberger's Clinical Electrocardiography: A Simplified Approach*, 10th ed. Philadelphia, Elsevier, 2024.)

TABLE 247-1 Differential Diagnosis of ST-Segment Elevations

Myocardial ischemia/infarction
Noninfarction transmural ischemia (e.g., Prinzmetal's syndrome)
Acute myocardial infarction
Due to atherosclerotic coronary occlusion
Due to nonatherosclerotic causes (e.g., takotsubo syndrome, coronary dissection)
Post-myocardial infarction (left ventricular motion abnormality/aneurysm)
Acute pericarditis
Normal variants (including benign "early repolarization" patterns)
Left ventricular hypertrophy/left bundle branch block ^a
Other (rarer)
Acute pulmonary embolism ^a
Brugada patterns (right bundle branch block–like morphology with ST elevations in right precordial leads)
Class 1C antiarrhythmic drugs ^a
DC cardioversion (transient)
Hypercalcemia ^a
Hyperkalemia ^a
Hypothermia (J [Osborn] waves)
Nonischemic myocardial injury
Myocarditis syndromes (infectious and noninfectious)
Tumor invading left ventricle
Trauma to ventricles

^aUsually localized to V₁–V₂ or V₃.

Source: Modified from AL Goldberger et al: *Goldberger's Clinical Electrocardiography: A Simplified Approach*, 10th ed. Elsevier, 2024.

ventricular hypertrophy, cardiomyopathies, myocarditis, and "stress cardiomyopathies" associated with takotsubo syndrome and cerebrovascular injury (particularly intracranial bleeds), among others causes. Diagnostic confusion may also occur when nonischemic T-wave inversions ("cardiac memory" effect) appear in normally conducted beats in patients with intermittent wide QRS complexes, most commonly due to ventricular pacing or to left bundle branch block.

METABOLIC FACTORS AND DRUG EFFECTS

A variety of metabolic abnormalities and pharmacologic agents alter the ECG and, in particular, cause changes in repolarization (ST-T-U) and sometimes QRS prolongation. Certain life-threatening electrolyte disturbances may be diagnosed initially and monitored from the ECG. *Hyperkalemia* produces a sequence of changes (Fig. 247-14), usually

beginning with narrowing and peaking (tenting) of the T waves. Further elevation of extracellular K⁺ leads to AV conduction disturbances, diminution in P-wave amplitude, and widening of the QRS interval. Severe hyperkalemia eventually causes cardiac arrest with a slow sinusoidal type of mechanism ("sine-wave" pattern) followed by asystole. *Hypokalemia* (Fig. 247-15) prolongs ventricular repolarization, often with prominent U waves. Prolongation of the QT interval is also seen with drugs that increase the duration of the ventricular action potential: class 1A antiarrhythmic agents and related drugs (e.g., quinidine, procainamide, tricyclic antidepressants, phenothiazines) and class III agents (e.g., amiodarone [Fig. 247-15], dofetilide, sotalol, ibutilide). Systemic *hypothermia* (Fig. 247-15) also prolongs repolarization, usually with a distinctive convex elevation of the J point (Osborn wave) and bradycardia. Marked QT prolongation, sometimes with deep, wide T-wave inversions, may occur with intracranial bleeds, particularly subarachnoid hemorrhage ("CVA T-wave" pattern) (Fig. 247-15). *Hypocalcemia* typically prolongs the QT interval (ST portion), whereas *hypercalcemia* shortens it (Fig. 247-16). Digitalis glycosides also shorten the QT interval, often with a characteristic "scooping" of the ST-T-wave complex (*digitalis effect*).

NONSPECIFIC ST-T CHANGES AND LOW QRS VOLTAGE

Many other factors are associated with ECG changes, particularly alterations in ventricular repolarization. T-wave flattening, minimal T-wave inversions, or slight ST-segment depression ("nonspecific ST-T-wave changes") may occur with a variety of electrolyte and acid-base disturbances, infectious or inflammatory processes, central nervous system disorders, endocrine abnormalities, many drugs, ischemia, hypoxia, and virtually any type of cardiopulmonary abnormality, in addition to physiologic changes (e.g., with posture or after meals). Low QRS voltage is arbitrarily defined as peak-to-trough QRS amplitudes of ≤5 mm in the six limb leads and/or ≤10 mm in the chest leads. Multiple factors may be responsible. Among the most serious include pericardial (Fig. 247-17) or pleural effusions, chronic obstructive pulmonary disease, cardiac amyloid, and anasarca.

ELECTRICAL ALTERNANS SYNDROMES

Electrical alternans—a beat-to-beat alternation in one or more components of the ECG signal—is a common type of nonlinear cardiovascular response to a variety of hemodynamic and electrophysiologic perturbations. Total electrical alternans (P-QRS-T) with sinus tachycardia is a relatively specific sign of pericardial effusion, usually with cardiac tamponade (Fig. 247-17). In contrast, pure repolarization

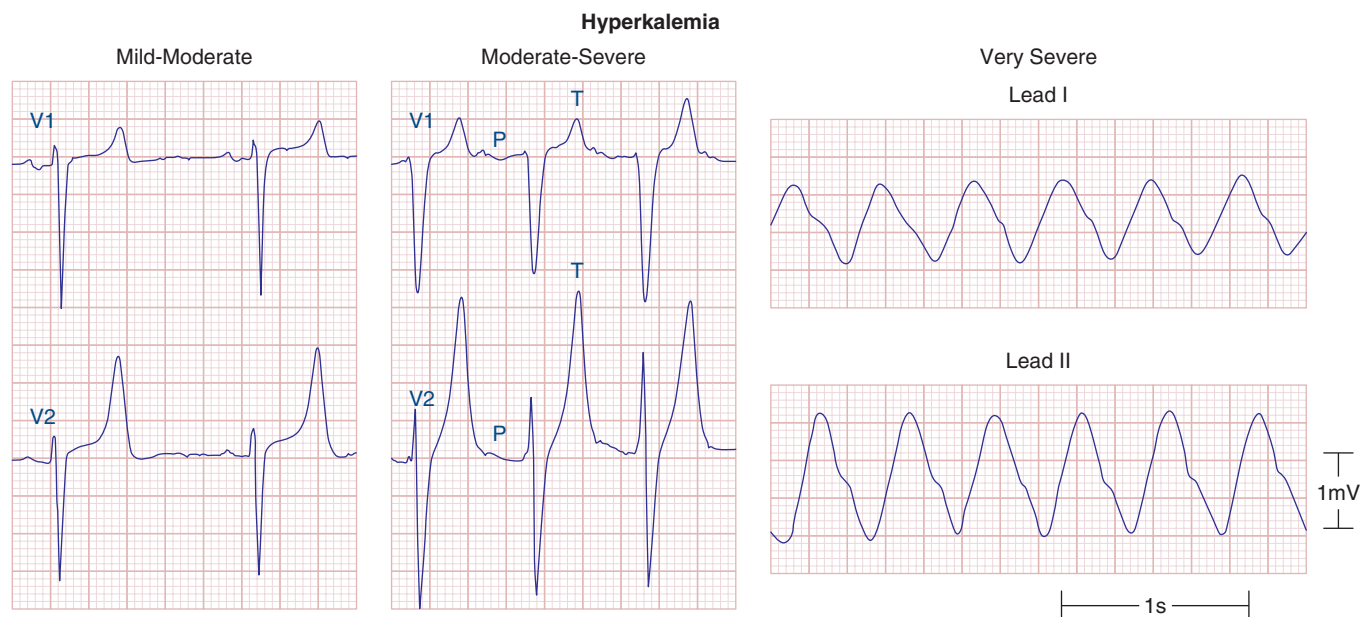


FIGURE 247-14 The earliest ECG change with hyperkalemia is usually peaking ("tenting") of the T waves. With further increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine-wave pattern leads to asystole unless emergency therapy is given. (Reproduced with permission from AL Goldberger et al: *Goldberger's Clinical Electrocardiography: A Simplified Approach*, 10th ed. Philadelphia, Elsevier, 2024.)

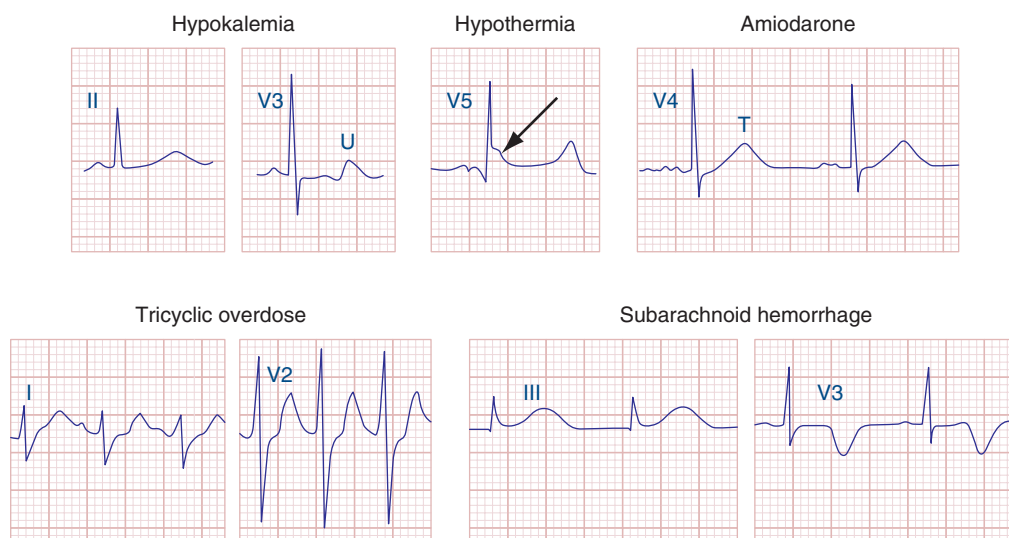


FIGURE 247-15 A variety of metabolic derangements, drug effects, and other factors may prolong ventricular repolarization with QT prolongation or prominent U waves. Prominent repolarization prolongation, particularly if due to hypokalemia, inherited “channelopathies,” or certain pharmacologic agents, indicates increased susceptibility to *torsades des pointes* ventricular tachycardia (Chap. 261). Marked systemic hypothermia is associated with a distinctive convex “hump” at the J point (Osborn wave, arrow) attributed to altered transmural ventricular action potential characteristics. Note QRS and QT prolongation along with sinus tachycardia in the case of tricyclic antidepressant overdose.

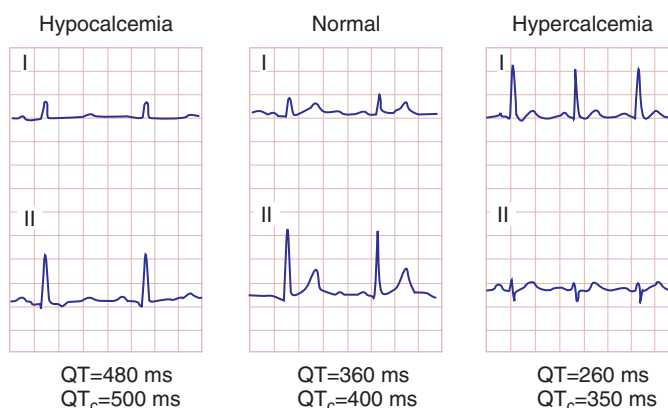


FIGURE 247-16 Prolongation of the Q-T interval (ST-segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment with relative or absolute shortening of the QT interval.

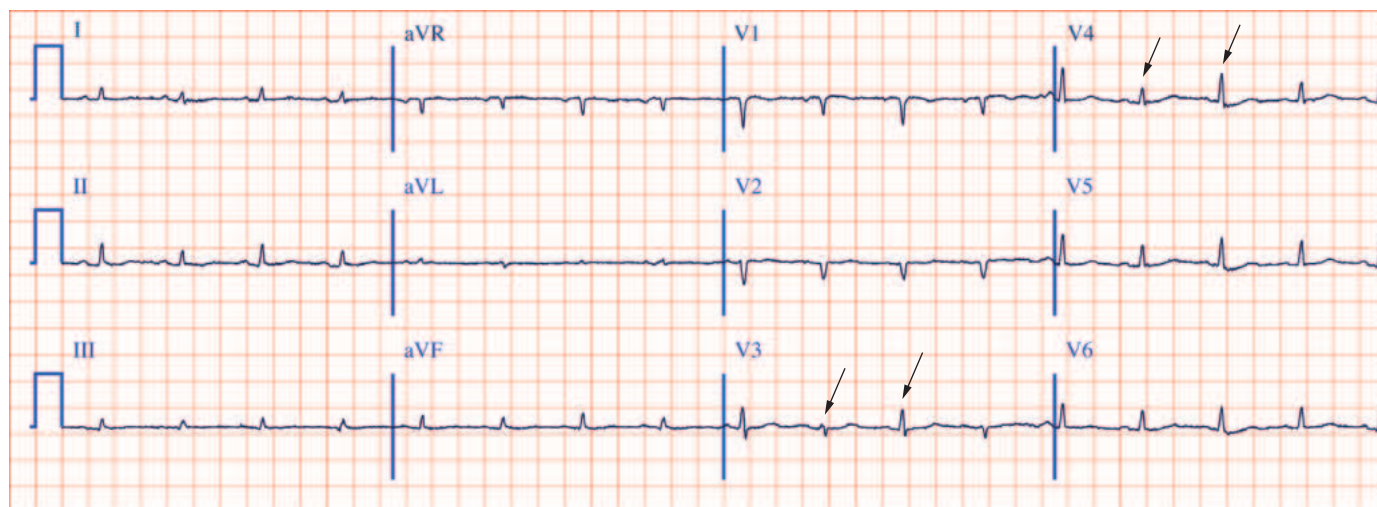


FIGURE 247-17 Classic triad of findings for pericardial effusion with cardiac tamponade: (1) sinus tachycardia; (2) low QRS voltages and (3) electrical alternans (best seen in leads V_3 and V_4 in this case; arrows). This triad is highly suggestive of pericardial effusion, usually with tamponade physiology, but is of limited sensitivity. (Adapted from LA Nathanson et al: ECG Wave-Maven. *ecg.bidmc.harvard.edu*.)

■ CLINICAL INTERPRETATION OF THE ECG

Accurate analysis of ECGs requires thoroughness and care. The patient's age, biologic sex, and clinical status should always be considered. Many mistakes in ECG interpretation are errors of omission. Therefore, a systematic approach is essential. The following 14 parameters should be analyzed carefully in every ECG: (1) standardization (calibration) and technical features (including lead placement and artifacts); (2) rhythm; (3) heart rate; (4) PR interval/AV conduction; (5) QRS interval; (6) QT/QT_c intervals; (7) mean QRS electrical axis; (8) P waves; (9) QRS voltages; (10) precordial R-wave progression; (11) abnormal Q waves; (12) ST segments; (13) T waves; and (14) U waves. Comparison with any previous ECGs is invaluable.

■ COMPUTERIZED ELECTROCARDIOGRAPHY

Computerized systems are widely used for storage and immediate retrieval of vast numbers of ECG records. Fully automated computerized ECG analyses still have major limitations and, therefore, should not be accepted without careful clinician review.

■ FURTHER READING

- COOK DA et al: Accuracy of physicians' electrocardiogram interpretations: A systematic review and meta-analysis. *JAMA Intern Med* 180:1461, 2020.
- GOLDBERGER AL et al: *Goldberger's Clinical Electrocardiography: A Simplified Approach*, 10th ed. Philadelphia, Elsevier, 2024.
- ISMAIL H et al: Neuromuscular disorders and the role of the clinical electrophysiologist. *J Am Coll Cardiol Clin Electrophysiol* 3:1069, 2017.
- MIRVIS DM, GOLDBERGER AL: Electrocardiography, in *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 12th ed, Libby P et al (eds). Philadelphia, Elsevier, 2021, pp. 141-174.
- NATHANSON LA et al: ECG Wave-Maven. Self-assessment program for students and physicians. Available at ecg.bidmc.harvard.edu. Accessed January 1, 2024.
- SHARMA S et al: International recommendations for electrocardiographic interpretation in athletes. *Eur Heart J* 39:1466, 2018.

These studies, often used in conjunction with exercise or pharmacologic stress testing, can be used independently or can provide complementary information for patient diagnosis or prognosis. In this chapter, we review the principles of each of these modalities and the utility and relative benefits of each for the most common cardiovascular diseases.

PRINCIPLES OF MULTIMODALITY CARDIAC IMAGING

■ ECHOCARDIOGRAPHY

Echocardiography uses high-frequency sound waves (ultrasound) to penetrate the body, reflect from relevant structures, and generate an image. The basic physical principles of echocardiography are identical to other types of ultrasound imaging, although the hardware and software are optimized for evaluation of cardiac structure and function. Early echocardiography machines displayed "M-mode" echocardiograms in which a single ultrasound beam was displayed over time on a moving sheet of paper (**Fig. 248-1, left panel**). Modern echocardiographic machinery uses phased array transducers that contain up to 512 elements and emit ultrasound in sequence. The reflected ultrasound is then sensed by the receiving elements, and images are generated by microprocessors that use information about the timing and magnitude of the reflected ultrasound to generate an image (**Fig. 248-1, right panel**). This sequence happens repeatedly in "real time" to generate moving images with frame rates that are typically >30 frames per second but can exceed 100 frames per second. The gray scale of the image features indicates the intensity of the reflected ultrasound; fluid or blood appears black, and highly reflective structures, such as calcifications on cardiac valves or the pericardium, appear white. Tissues such as myocardium appear gray, and tissues such as muscle display a unique speckle pattern.

The spatial resolution of ultrasound is dependent on the frequency of the ultrasound (inverse of wavelength). The higher the frequency of the ultrasound beam, the greater the spatial resolution and ability to discern small structures, but at the cost of penetration, which is decreased at higher frequencies. Thus, higher frequencies are used in pediatric imaging or transesophageal echocardiography where the transducer is typically much closer to the structures being interrogated.

Three-dimensional ultrasound transducers use a waffle-like matrix array transducer and receive a pyramidal data sector. Three-dimensional echocardiography is being increasingly used for assessment of congenital heart disease and valves, particularly with transesophageal echocardiography, although current image quality lags behind two-dimensional (2D) ultrasound (**Fig. 248-2**).

In addition to the generation of 2D images that provide information about cardiac structure and function, echocardiography can be used to interrogate blood flow within the heart and blood vessels by using the Doppler principle to ascertain the velocity of blood flow. When ultrasound emitted from a transducer reflects off red blood cells that are moving toward the transducer, the reflected ultrasound will return at a slightly higher frequency than emitted; the opposite is true when flow moves away from the transducer. That frequency difference, termed the Doppler shift, is directly related to the velocity of the flow of the red blood cells. The velocity of blood flow between two chambers will be directly related to the pressure gradient between those chambers. A modified form of the Bernoulli equation,

$$p = 4v^2$$

where p = the pressure gradient and v = the velocity of blood flow in meters per second, can be used to calculate this pressure gradient in most clinical circumstances. This principle can be used to determine the pressure gradient between chambers and across valves and has become central to the quantitative assessment of valvular heart disease.

There are three types of Doppler ultrasound that are typically used in standard echocardiographic examinations: spectral Doppler, which consists of both pulsed wave Doppler and continuous wave Doppler, and color flow Doppler. Both types of spectral Doppler will display a waveform representing the velocity of blood flow, with time on the horizontal axis and velocity on the vertical axis. Pulsed wave Doppler

248 Noninvasive Cardiac Imaging: Echocardiography, Nuclear Cardiology, and Magnetic Resonance/Computed Tomography Imaging

Marcelo F. DiCarli, Raymond Y. Kwong,
Scott D. Solomon

The ability to image the heart and blood vessels noninvasively has been one of the greatest advances in cardiovascular medicine since the development of the electrocardiogram (ECG). Cardiac imaging complements history taking and physical examination, blood and laboratory testing, and exercise testing in the diagnosis and management of most diseases of the cardiovascular system. Modern cardiovascular imaging consists of echocardiography (cardiac ultrasound), nuclear scintigraphy including positron emission tomography (PET) imaging, magnetic resonance imaging (MRI), and computed tomography (CT).

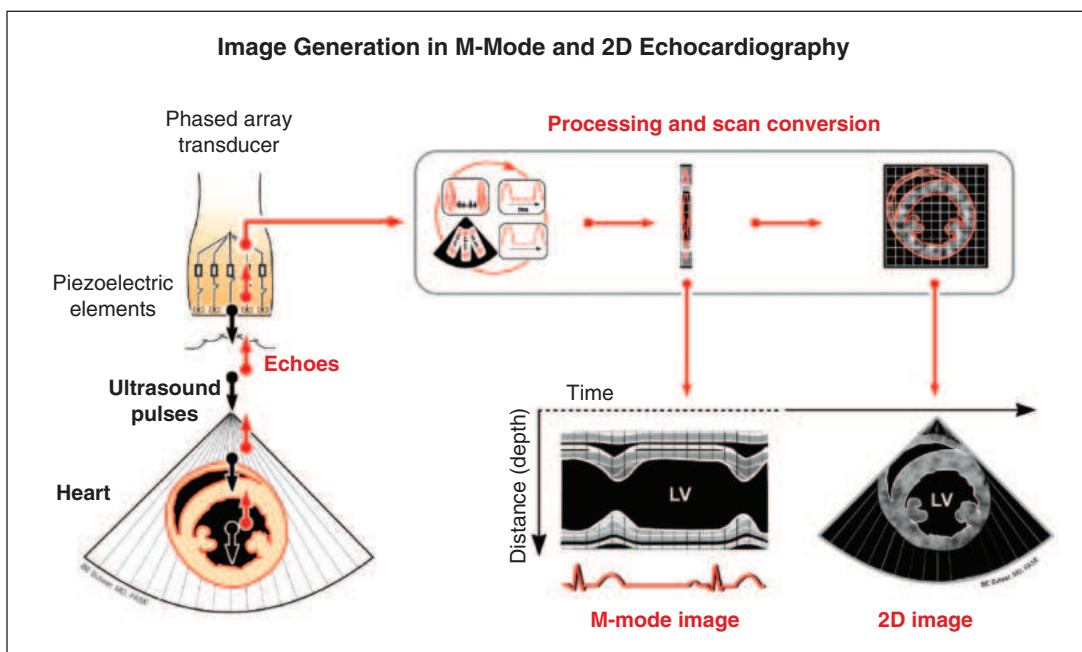


FIGURE 248-1 Principle of image generation in two-dimensional (2D) echocardiography. An electronically steerable phased-array transducer emits ultrasound from piezoelectric elements, and returning echoes are used to generate a 2D image (right) using a scan converter. Early echocardiography machines used a single ultrasound beam to generate an “M-mode” echocardiogram (see text), although modern equipment generates M-mode echocardiograms digitally from the 2D data. LV, left ventricle.

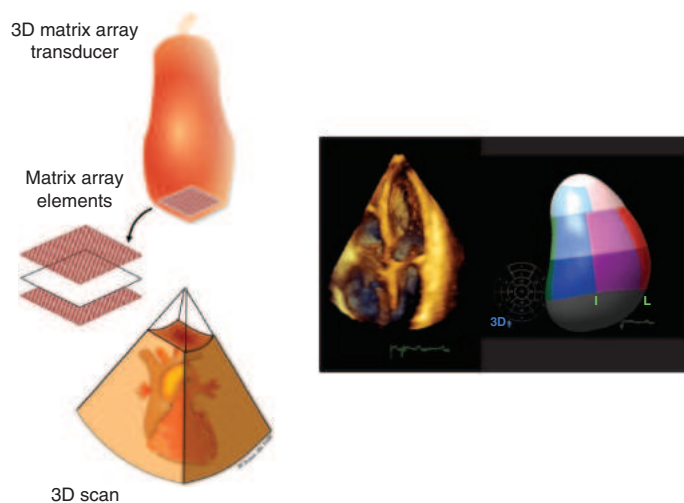


FIGURE 248-2 Three-dimensional (3D) probe and 3D image.

is used to interrogate relatively low velocity flow and has the ability to determine blood flow velocity at a particular location within the heart. Continuous wave Doppler is used to assess high velocity flow but can only identify the highest velocity in a particular direction and cannot interrogate the velocity at a specific depth location. Both techniques can only accurately assess velocities that are in the direction of the ultrasound scan lines, and velocities that are at an angle to the direction of the ultrasound beam will be underestimated. Color flow Doppler is a form of pulsed wave Doppler in which the velocity of blood flow is color encoded according to a scale and superimposed on a 2D gray-scale image in real time, giving the appearance of real-time flow within the heart. The Doppler principle can also be used to assess the velocity of myocardial motion, which is a sensitive way to assess myocardial function (Fig. 248-3). A standard full transthoracic echocardiographic examination consists of a series of 2D views made up of different imaging planes from various scanning locations and spectral and color flow Doppler assessment.

Transesophageal Echocardiography Transesophageal echocardiography is a form of echocardiography in which the transducer

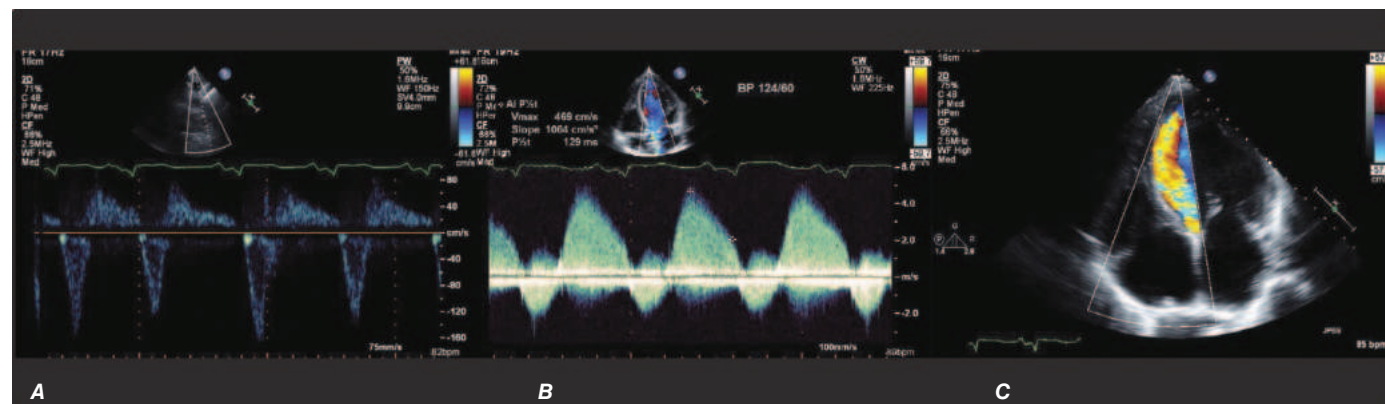


FIGURE 248-3 Three types of Doppler ultrasound. A and B. Pulsed and continuous wave Doppler waveforms with time on horizontal axis and velocity of blood flow on vertical axis. **C.** Color flow Doppler, where velocities are encoded by colors according to scale on right side of screen and superimposed on a two-dimensional grayscale image.



FIGURE 248-4 Two examples of handheld ultrasound equipment: V-Scan (General Electric, left) and Sonosite (right).

is located on the tip of an endoscope that can be inserted into the esophagus. This procedure allows closer, less obstructed views of cardiac structures, without having to penetrate through chest wall, muscle, and ribs. Because less penetration is needed, a higher frequency probe can be used, and image quality and spatial resolution are generally higher than with standard transthoracic imaging, particularly for structures that are more posterior. Transesophageal echocardiography has become the test of choice for assessment of small lesions in the heart such as valvular vegetations, especially in the setting of a prosthetic valve disease, and intracardiac thrombi, including assessment of the left atrial appendage, which is difficult to visualize with standard transthoracic imaging, and for assessment of congenital abnormalities. Transesophageal echocardiography requires both topical and systemic anesthesia, generally conscious sedation, and carries additional risks such as potential damage to the esophagus, including the rare possibility of perforation, aspiration, and anesthesia-related complications. Patients generally need to give consent for transesophageal echocardiography and be monitored during and after the procedure. Transesophageal echocardiography can be carried out in intubated patients and is routinely used for intraoperative monitoring during cardiac surgery.

Stress Echocardiography Stress echocardiography is routinely used to assess cardiac function during exercise and can be used to identify myocardial ischemia or to assess valvular function under exercise conditions. Stress echocardiography is typically performed in conjunction with treadmill or bicycle exercise testing but can also be performed using pharmacologic stress most typically with an intravenous infusion of dobutamine (see section on stress imaging below).

Point-of-Care/Handheld Echocardiography Whereas typical echocardiographic equipment is large, bulky, and expensive, small handheld or point-of-care ultrasound (POCUS) equipment developed over the last decade now offers diagnostic quality imaging in a package small enough to be carried on rounds (**Fig. 248-4**). These relatively

inexpensive point-of-care devices are gaining full diagnostic capabilities and currently represent an excellent screening tool if used by an experienced operator. As these units become even smaller and less expensive, they are being increasingly used not just by cardiologists, but also by emergency medicine physicians, intensivists, anesthesiologists, and internists.

Nevertheless, echocardiography is a nontomographic modality. The image obtained is dependent on the skill of the operator who, holding a transducer, identifies standard views from which measurements can be made. Images that are obtained off-axis can result in incorrect measurements such as chamber volumes or ejection fraction. As point-of-care echocardiography becomes more commonplace, practitioners will need sufficient training to obtain and interpret images. Artificial intelligence has been incorporated into several devices to help guide the user to obtain optimal images and to help with interpretation (see below). Myocardial strain or deformation imaging has emerged as an alternative way to assess cardiac

contractile performance. Global and/or regional myocardial strain can be assessed by either Doppler or, more commonly, 2D echocardiography. Global longitudinal strain is assessed from the apical view and calculated as the endocardial perimeter length in end-diastole minus the endocardial perimeter length in end-systole and divided by the endocardial perimeter length in end-diastole. It is a more robust measure of contractile function than volumetric-based ejection fraction and has been shown to be predictive of outcome in a variety of cardiac diseases, including heart failure and following myocardial infarction.

RADIONUCLIDE IMAGING

Radionuclide imaging techniques are commonly used for the evaluation of patients with known or suspected coronary artery disease (CAD), including for initial diagnosis and risk stratification as well as the assessment of myocardial viability. In addition, radionuclide imaging is commonly used in the evaluation of patients with suspected cardiac amyloidosis, myocardial and vascular inflammation, and infective endocarditis. These techniques use small amounts of radiopharmaceuticals (**Table 248-1**), which are injected intravenously and trapped in the heart and/or vascular cells. Radioactivity within the heart and vasculature decays by emitting gamma rays. The interaction between these gamma rays and the detectors in specialized scanners (single-photon emission computed tomography [SPECT] and PET) creates a scintillation event or light output, which can be captured by digital recording equipment to form an image of the heart and vasculature. Like CT and MRI, radionuclide images also generate tomographic (three-dimensional) views of the heart and vasculature.

Radiopharmaceuticals Used in Clinical Imaging Table 248-1 summarizes the most commonly used radiopharmaceuticals in clinical SPECT and PET imaging.

Protocols for Stress Myocardial Perfusion Imaging Both exercise and pharmacologic stress can be used for myocardial

TABLE 248-1 Radiopharmaceuticals for Clinical Nuclear Cardiology

RADIOPHARMACEUTICAL	IMAGING TECHNIQUE	PHYSICAL HALF-LIFE	APPLICATION
Technetium-99m sestamibi	SPECT	6 h	Myocardial perfusion imaging
Technetium-99m tetrofosmin	SPECT	6 h	Myocardial perfusion imaging
Thallium-201	SPECT	72 h	Myocardial perfusion imaging
Iodine-123 metaiodobenzylguanidine (MIBG)	SPECT	13 h	Cardiac sympathetic innervation
Rubidium-82	PET	76 s	Myocardial perfusion imaging
¹³ N-ammonia	PET	10 min	Myocardial perfusion imaging
¹⁸ F-fluorodeoxyglucose	PET	110 min	Myocardial viability, infection and inflammation imaging
Technetium-99m pyrophosphate (PYP), technetium-99m hydroxymethylene diphosphonate (HMDP), technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD)	SPECT	6 h	Cardiac amyloidosis

Abbreviations: PET, positron emission tomography; SPECT, single-photon emission computed tomography.

perfusion imaging. Exercise stress is generally preferred because it is physiologic and provides additional clinically important information (i.e., clinical and hemodynamic responses, ST-segment changes, exercise duration, and functional status). However, submaximal effort will lower the sensitivity of the test and should be avoided, especially if the test is requested for initial diagnosis of CAD. In patients who are unable to exercise or who exercise submaximally, pharmacologic stress offers an adequate alternative to exercise stress testing. Pharmacologic stress can be accomplished either with coronary vasodilators, such as adenosine, dipyridamole, or regadenoson, or β_1 -receptor agonists, such as dobutamine. For patients unable to exercise, vasodilators are the most commonly used stress agents in combination with myocardial perfusion imaging. Dobutamine is a potent β_1 -receptor agonist that increases myocardial oxygen demand by augmenting contractility, heart rate, and blood pressure such as exercise. It is generally used as an alternative to vasodilator stress in patients with chronic pulmonary disease, in whom vasodilators may be contraindicated. Dobutamine is also commonly used as a pharmacologic alternative to stress testing in stress echocardiography.

Myocardial Perfusion and Viability Imaging Protocols
Imaging protocols are tailored to the individual patient based on the clinical question, patient's risk, ability to exercise, body mass index, and other factors.

For SPECT imaging, technetium-99m (^{99m}Tc)-labeled tracers are the most used imaging agents because they are associated with the best image quality and the lowest radiation dose to the patient (Fig. 248-5). Selection of the protocol (stress-only, single-day, or 2-day) depends on the patient and clinical question. After intravenous injection, myocardial uptake of ^{99m}Tc -labeled tracers is rapid (1–2 min). After uptake, these tracers become trapped intracellularly in mitochondria and show minimal change over time. This is why ^{99m}Tc tracers can be helpful in patients with chest pain of unclear etiology occurring at rest because patients can be injected while having chest pain and imaged sometime later after symptoms subside. Indeed, a normal myocardial perfusion study following a rest injection in a patient with active chest pain effectively excludes myocardial ischemia as the cause of chest

pain (high negative predictive value). While used commonly in the past for perfusion imaging, thallium-201 protocols are now rarely used because they are associated with a higher radiation dose to the patient.

PET myocardial perfusion imaging is an alternative to SPECT and is associated with improved diagnostic accuracy and lower radiation dose to patients (Table 248-1). The ultra-short half-life of some PET radiopharmaceuticals in clinical use (e.g., rubidium-82) is the primary reason why imaging is generally combined with pharmacologic stress, as opposed to exercise. However, exercise is possible for relatively longer-lived radiotracers (e.g., ^{13}N -ammonia). PET imaging protocols are typically faster than SPECT, but more expensive. In comparison to SPECT, PET has improved spatial and contrast resolution and provides absolute measures of myocardial perfusion (in mL/min per gram of tissue), thereby providing the patients' regional and global coronary flow reserve. The latter helps improve diagnostic accuracy and risk stratification, especially in obese patients, women, and higher risk individuals (e.g., diabetes mellitus) (Fig. 248-6). Contemporary PET and SPECT scanners are combined with a CT scanner (so-called *hybrid PET/CT* and *SPECT/CT*). CT is used primarily to guide patient positioning in the field of view and for correcting inhomogeneities in radiotracer distribution due to attenuation by soft tissues (so-called *attenuation correction*). However, it can also be used to obtain diagnostic data including coronary artery calcium (CAC) score and/or CT coronary angiography (discussed below).

For the evaluation of myocardial viability in patients with ischemic cardiomyopathy, myocardial perfusion imaging (with SPECT or PET) is usually combined with metabolic imaging (i.e., fluorodeoxyglucose [FDG] PET). In hospital settings lacking access to PET scanning, thallium-201 SPECT imaging is an excellent alternative. FDG-PET is also used in the evaluation of myocardial and vascular inflammation and in patients with suspected infective endocarditis.

Bone scintigraphy with SPECT is currently used for the evaluation of patients with suspected cardiac amyloidosis. As discussed below under applications in new-onset heart failure, bone-seeking ^{99m}Tc radiotracers (Table 248-1) are currently used to diagnose transthyretin cardiac amyloidosis with high accuracy.

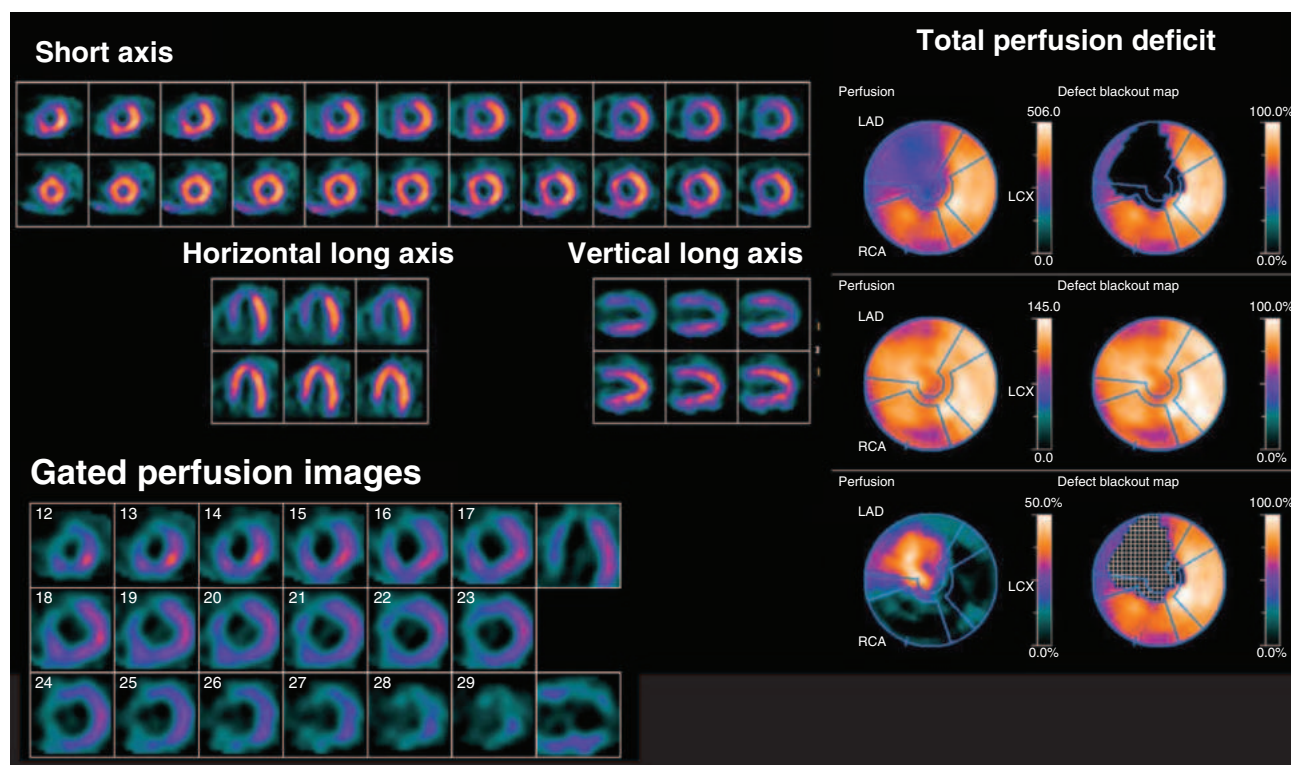


FIGURE 248-5 Tomographic stress (top of each pair) and rest myocardial perfusion images with technetium-99m sestamibi single-photon emission computed tomography imaging demonstrating a large perfusion defect throughout the anterior and anteroseptal walls. The *right panel* demonstrates the quantitative extent of the perfusion abnormality at stress (*top bull's-eye*) and at rest (*middle bull's-eye*), and the extent of defect reversibility (*lower bull's-eye*). The *lower left panel* demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction.

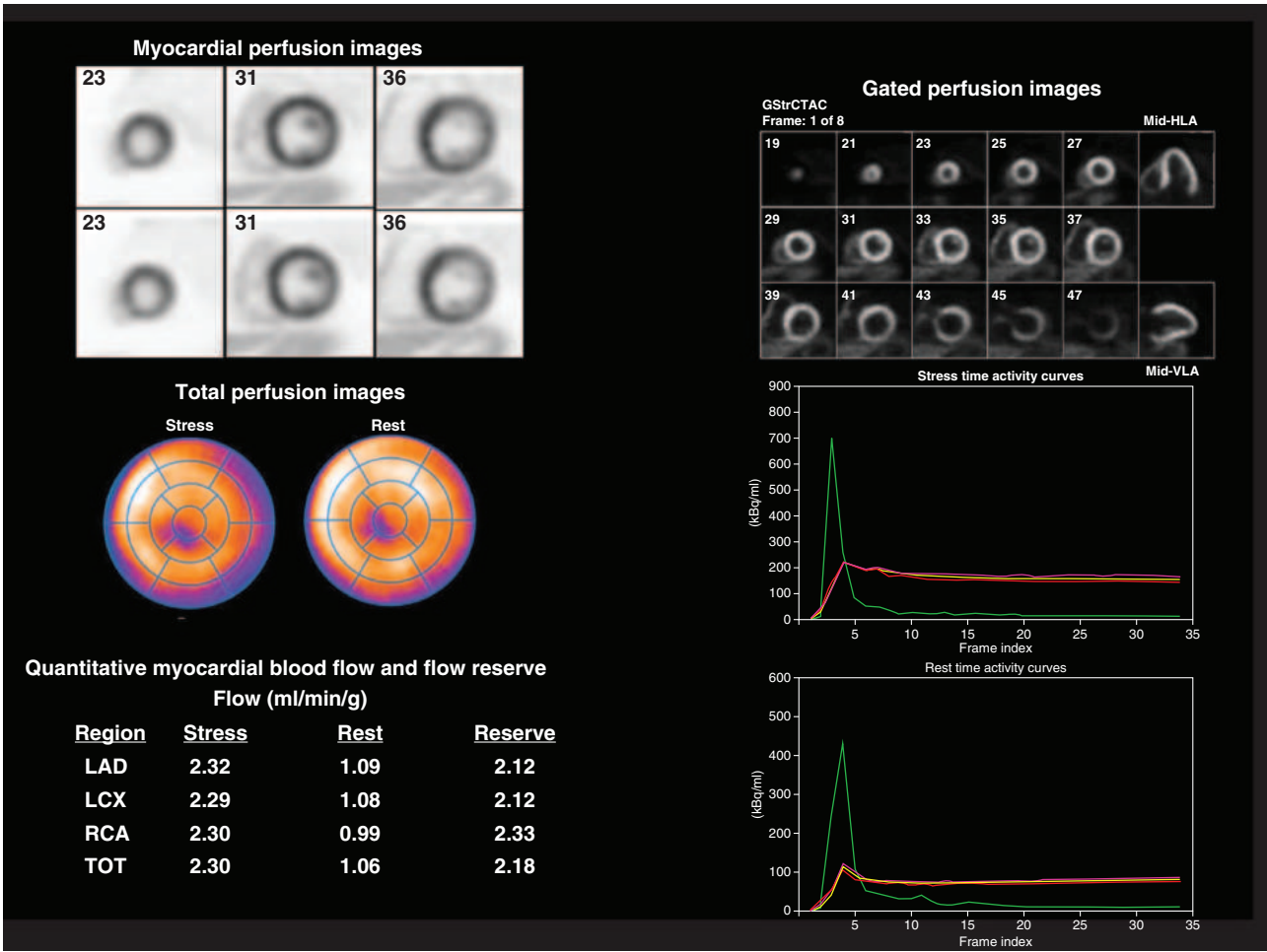


FIGURE 248-6 Multidimensional cardiac imaging protocol with positron emission tomography. The *left upper panel* demonstrates stress and rest short-axis images of the left and right ventricles demonstrating normal regional myocardial perfusion. The *middle panel* demonstrates the quantitative bull's-eye display to evaluate the extent and severity of perfusion defects. The *lower right panel* illustrates the time-activity curves for quantification of myocardial blood flow. The *right upper panel* demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TOT, total left ventricle.

CARDIAC COMPUTED TOMOGRAPHY

CT acquires images by passing a thin x-ray beam through the body at many angles to generate cross-sectional images. The x-ray transmission measurements are collected by a detector array and digitized into pixels that form an image. The grayscale information in individual pixels is determined by the attenuation of the x-ray beam along its path by tissues of different densities, referenced to the value for water in units known as Hounsfield units. In the resulting CT images, bone appears bright white, air is black, and blood and muscle show varying shades of gray. However, due to the limited contrast between cardiac chambers and vascular structures, iodinated contrast agents are necessary for most cardiovascular indications. Cardiac CT produces tomographic images of the heart and surrounding structures. With modern CT scanners, a three-dimensional dataset of the heart can be acquired in 5–15 s with submillimeter spatial resolution.

CT Calcium Scoring CT calcium scoring is the simplest application of cardiac CT and does not require administration of iodinated contrast. The presence of coronary artery calcification has been associated with increased burden of atherosclerosis and cardiovascular mortality. Coronary calcium is then quantified (e.g., Agatston score) and categorized as minimal (0–10), mild (10–100), moderate (100–400), or severe (>400) (Fig. 248-7). CAC scores are then normalized by age and gender and reported as percentile scores. Population-based studies in asymptomatic cohorts have reported high cardiac prognostic value of CT calcium score. With appropriate techniques, the radiation dose associated with CAC scanning is very low (~1–2 mSv).

CT Coronary Angiography Coronary CT angiography (CTA) is a clinically important alternative to stress testing in selected patients with suspected CAD. Imaging of the coronary arteries by CT is challenging because of their small luminal size and because of cardiac and respiratory motion. Respiratory motion can be reduced by breath-holding, and cardiac motion is best reduced by slowing the patient's heart rate, ideally to under 60 beats/min, using intravenous or oral beta blockade or other rate-lowering drugs. When performing a coronary CTA, image quality is further enhanced using sublingual nitroglycerin to enlarge the coronary lumen just prior to contrast injection. Imaging the whole-heart volume is synchronized to the administration of weight-based and appropriately timed intravenous iodinated contrast. Image acquisition is linked to the timing of the cardiac cycle through ECG triggering. The resulting images are then postprocessed using a three-dimensional workstation, which facilitates interpretation of the coronary anatomy and estimation of the severity of atherosclerosis (Fig. 248-7). A modified version of the enhanced protocol outlined for coronary CTA is used for the evaluation of patients with structural heart disease, especially for preprocedural planning of those undergoing transcatheter valve replacement.

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) imaging is based on imaging of protons in hydrogen, which is an advantage, given the abundance of water in the human body. When the body is placed inside an MRI scanner, protons in different tissues, such as in simple fluid or complex macromolecules such as fat or protein, interact with the magnetic field

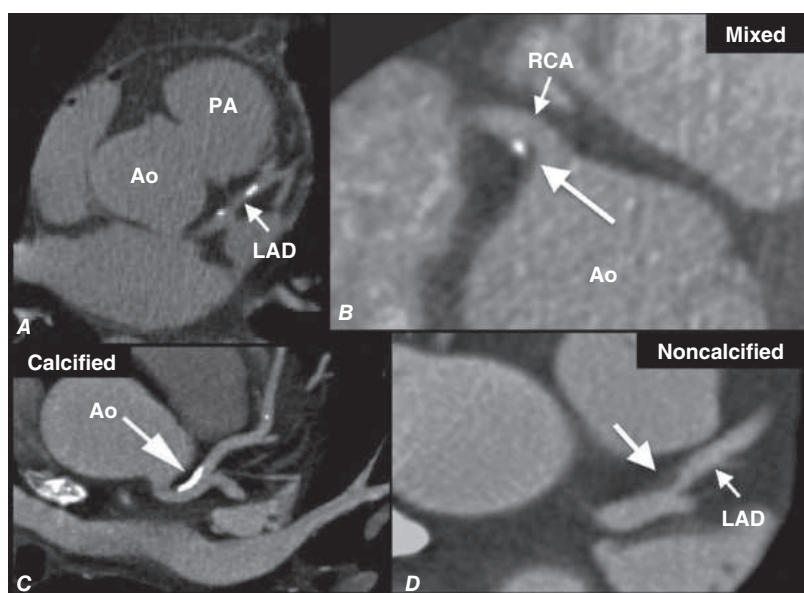


FIGURE 248-7 Examples of non-contrast- and contrast-enhanced coronary imaging with computed tomography (CT). **A**, Calcified coronary plaques in the distal left main and proximal left anterior descending coronary artery (LAD) in a noncontrast cardiac CT scan. Calcium deposits are dense and present as bright white structures on CT, even without contrast enhancement. **B, C, and D**, Different types of atherosclerotic plaques on contrast-enhanced CT scans. Importantly, noncalcified plaques are evident only on contrast-enhanced CT scans. AO, aorta; PA, pulmonary artery; RCA, right coronary artery.

at their unique frequencies. A set of orthogonal gradient coils in the scanner is designed to locate protons spatially so that radiofrequency (RF) energy pulses can be delivered to select imaging planes of interest. Once the RF pulses stop, the energy absorbed will be released, collected by the phased-array receiver coils placed on the patient's body surface, digitally recorded in a data matrix known as the K-space, then reconstructed into a magnetic resonance image. The large arrays of software methods of delivering RF pulses are known as pulse sequences, which aim to extract different types of cardiac structural or physiologic information. In CMR, T1-weighted pulse sequences are most common, and they assess cardiac structure and function, blood flow, and myocardial perfusion with pharmacologic stress. T2-weighted and T2*-weighted pulse sequences, on the other hand, evaluate myocardial edema and myocardial iron infiltration, respectively. In recent years, T1 and T2 mapping have become routinely used in experienced centers in quantifying myocardial tissue characteristics, with T1 mapping most commonly used to scale the spectrum of myocardial inflammation or fibrosis and T2 mapping for myocardial edema. Using a combination of these methods above, a CMR can accurately assess cardiac structures and function, myocardial infarction and viability, ischemia, and infiltration. Currently, the most common indications for a CMR include assessing the etiology of cardiomyopathy, myocardial ischemia from chest pain syndromes, myocardial viability for benefits of revascularization, pericardial diseases, and myocardial substrates of arrhythmias. Vector ECG-gating and repetitive patient breath-holding are used by convention to suppress cardiac and respiratory motions, respectively. However, with technical advent, rapid data collection algorithms and diaphragmatic position gating have eliminated the need for ECG gating and breath-holding in challenging situations. A list of common pulse sequences used in CMR is shown in [Table 248-2](#).

ASSESSMENT OF CARDIAC STRUCTURE AND FUNCTION

Echocardiography, CMR, and cardiac CT are all capable of assessing cardiac structure and function, although echocardiography is generally considered the primary imaging method for these assessments. Radionuclide imaging can also be used to assess left ventricular regional and global systolic function. Echocardiography is most often used to assess the size of all four chambers and thickness of ventricular walls, which are affected by both cardiac and systemic diseases.

The structure of the left ventricle is generally assessed by determining its volume and mass. Left ventricular volumes can be easily

estimated from 2D echocardiography by using methods incorporating geometric assumptions. The accuracy of these echocardiographic methods is reduced when foreshortening of the imaging plane leads to underestimation of volumes. Moreover, these methods require accurate delineation of the endocardial border. In this regard, high-resolution tomographic techniques such as CMR or cardiac CT are more accurate for volumetric assessment. Three-dimensional (3D) echocardiography does not require any geometric assumptions about the left ventricle for quantification of volumes and ejection fraction. However, 3D echocardiographic imaging requires substantial expertise and currently is not widely used in practice.

Left ventricular dilatation is common to several cardiac diseases. For example, regional dysfunction secondary to myocardial infarction can ultimately lead to progressive ventricular dilatation or remodeling. Although dilatation often begins in the region affected by the

TABLE 248-2 Clinical Cardiac Magnetic Resonance Pulse Sequences and Their Application

PULSE SEQUENCE	KEY IMAGING INTERESTS
Cardiac Morphology	
Still frame imaging (black or bright blood)	Cardiac structures
Cardiac Function	
Cine imaging	Left ventricular volume and function
Cine myocardial tagging	Left ventricular deformation (strain)
Blood Flow Imaging	
Velocity-encoded phase contrast	Cardiac and great vessel flow
Stress Testing	
Myocardial perfusion imaging	Regional myocardial blood flow
Cine imaging	Regional wall motion
Myocardial Tissue Characterization	
Late gadolinium enhancement	Myocardial infarction and infiltrative disease
T2-weighted imaging	Myocardial edema
Iron content imaging	Myocardial iron infiltration
Magnetic Resonance Angiography	
Aorta, peripheral and coronary arteries	Luminal stenosis and vessel wall remodeling

infarction, subsequent compensatory dilatation can occur in remote myocardial regions as well. The presence of regional wall motion abnormalities associated with ventricular thinning (reflecting scar) in a coronary distribution is strongly suggestive of an ischemic etiology. Regional wall motion can be accurately assessed by echocardiography, CMR, and cardiac CT. Direct assessment of infarcted myocardium is possible with both CMR (evident as areas of late gadolinium enhancement [LGE]) and radionuclide imaging (as assessed by regional perfusion or metabolic defects at rest). CMR can be particularly useful in determining etiology of cardiomegaly and ventricular dysfunction, with LGE in coronary distributions being nearly pathognomonic for infarction ([Video 248-1](#)).

More global ventricular dilatation is seen in cardiomyopathy and dilatation due to valvular heart disease. Idiopathic, nonischemic cardiomyopathies will typically result in global ventricular dilatation and dysfunction, with thinning of the walls. Patients with substantial ventricular dyssynchrony due to conduction abnormalities will have a typical pattern of contraction (e.g., delay of contraction of the lateral wall with left bundle branch block). As discussed later in this chapter, regurgitant lesions of either the mitral or aortic valves can lead to substantial ventricular dilatation, and assessment of ventricular size is integral in the evaluation and timing of surgical correction. Because changes in ventricular size are used clinically to determine which patients should undergo valve surgery, accurate assessment of changes in ventricular size is essential. Although serial echocardiography can provide these data, serial assessment by CMR may be more accurate when appreciation of subtle changes over time is important.

Left ventricular wall thickness and mass are also important measures of cardiac and systemic disease. The left ventricle will hypertrophy under any condition in which its afterload is increased, including conditions that obstruct outflow, such as aortic stenosis, hypertrophic cardiomyopathy, and subaortic membranes; in postcardiac aortic obstruction seen in coarctation; or in systemic conditions characterized by increased afterload, such as hypertension. The pattern of ventricular hypertrophy can change depending on the etiology. Aortic stenosis and hypertension are typically characterized by concentric hypertrophy, in which the ventricular walls thicken “concentrically” and cavity size is usually small. In volume overload conditions such as mitral or aortic regurgitation, there may be minimal increase in ventricular wall thickness, but substantial ventricular dilatation leads to marked increases in left ventricular mass.

Ventricular wall thickness can be measured, and ventricular mass can be calculated by either echocardiography or CMR. Although radionuclide imaging and cardiac CT can also provide measures of left ventricular mass, they are not generally used for this purpose. Although measurement of wall thickness with echocardiography is relatively straightforward and accurate, determining left ventricular mass by echocardiography requires using one of several formulas that consider both wall thickness and ventricular cavity dimensions. Assessment of left ventricular mass volumetrically by CMR has the advantage of not requiring geometric assumptions and is thus more accurate than echocardiography.

■ ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC FUNCTION

Assessment of ejection fraction, or the percentage of blood ejected with each beat, has been the primary method to assess systolic function and is generally calculated by subtracting end-systolic volume from end-diastolic volume and dividing by end-diastolic volume. All cardiac imaging modalities can provide direct measurements of left ventricular ejection fraction (LVEF). As discussed above, tomographic techniques (e.g., CMR, CT, and radionuclide imaging) are generally more accurate and reproducible than echocardiography because there are no geometric assumptions and these techniques are not dependent on operator skill, although echocardiography remains the most utilized method. A LVEF of 55% or greater is generally considered normal, and an LVEF of 50–55% is considered in the low-normal range, although these can vary widely, and normal ejection fraction tends to be higher in women than in men.

Newer methods to assess systolic function, such as myocardial strain or deformation imaging using speckle-tracking methods on echocardiography, myocardial tagging, and more recently, feature tracking on CMR, can provide a more sensitive approach to the detection of systolic dysfunction, in part because these measures are geometric assumption-independent. Additional assessments based on these novel methods include assessment of myocardial twist and torsion. Regional strain patterns can differ in various diseases. For example, in subtypes of cardiac amyloidosis, it is common to see a reduction in myocardial strain at the base of the heart with relative sparing of the apex. Strain imaging is being increasingly utilized in conditions such as valvular heart disease and early detection of cardiotoxicity following chemotherapy and/or radiation therapy. In addition to the estimation or calculation of ejection fraction, stroke volume can be assessed by any of the imaging methods by subtracting the end-systolic volume from the end-diastolic volume or by quantifying forward flows using echocardiographic Doppler methods or phase-contrast CMR imaging. They offer an estimated measure of cardiac output other than LVEF.

■ ASSESSMENT OF LEFT VENTRICULAR DIASTOLIC FUNCTION

Echocardiography remains the primary method for clinical assessment of diastolic function, in part because echocardiography has the highest temporal resolution of all the imaging techniques. Recent advances in Doppler tissue imaging allow for accurate assessment of the velocity of myocardial wall motion by assessing the excursion of the mitral annulus in diastole. Mitral annular relaxation velocity, or E' , is inversely related to the time constant of relaxation, τ , and has been shown to have prognostic significance in patients with heart failure. Dividing the standard mitral inflow maximal velocity, E , by the mitral annular relaxation velocity yields E/E' , which has been shown to correlate with left ventricular filling pressures. The utility of standard E and A wave ratios for assessment of diastolic function has been questioned. Mitral deceleration time can be a useful measure if very short (<150 ms), suggesting restrictive physiology and severe diastolic dysfunction. Left atrial volume is considered an integrator of diastolic function, and minimal volume may be more reflective of left ventricular filling pressures than maximal volume. Several grading methods for diastolic function have been proposed that take into account a number of diastolic parameters, including Doppler tissue-based relaxation velocities, pulmonary venous Doppler, and left atrial size ([Fig. 248-8](#)). Diastolic function worsens with aging, and most diastolic parameters need to be adjusted for age.

■ ASSESSMENT OF RIGHT VENTRICULAR FUNCTION

Right ventricular size and function have been shown to be prognostically important in a variety of conditions, and can be assessed by echocardiography, CMR, CT, or radionuclide imaging methods. CMR is considered the most accurate noninvasive technique to evaluate the structure and ejection fraction of the right ventricle ([Video 248-2](#)). Assessment of the right ventricle by echocardiography has generally been qualitative, owing in part to the unusual geometry of the right ventricle. However, several quantitative methods are available for assessment of right ventricular function, including fractional area change ($FAC = [\text{diastolic area} - \text{systolic area}] / \text{diastolic area}$), which has been shown to correlate with outcomes in heart failure and after myocardial infarction. Excursion of the tricuspid annulus (tricuspid annular plane systolic excursion [TAPSE]) is another method to assess right ventricular function, although it is mostly used in research settings.

Abnormalities of right ventricular size and function are generally secondary to either diseases that affect the right ventricle intrinsically or diseases in which the right ventricle responds to abnormalities elsewhere in the heart or pulmonary vasculature. Intrinsic diseases that affect the right ventricle include congenital abnormalities, including hypoplastic right ventricle and arrhythmogenic right ventricular dysplasia, and acquired conditions, such as right ventricular infarction

and infiltrative diseases. Right ventricular dilatation can occur due to both chronic and acute processes. Long-standing pulmonary hypertension or pulmonary outflow tract obstruction leads to right ventricular hypertrophy and ultimately dilatation. An acute process that can cause profound right ventricular dilatation and dysfunction is acute pulmonary embolism. In the setting of acute occlusion of a pulmonary artery or branch, an acute rise in pulmonary vascular resistance causes a previously normal right ventricle to dilate and fail due to the increased afterload. In acute pulmonary embolism, right ventricular dilatation and dysfunction are signs of substantial hemodynamic compromise and are associated with a marked increased risk of death. In addition to right ventricular dilatation, acute pulmonary embolism is often associated with a specific pattern of regional right ventricular dysfunction, commonly referred to as the McConnell sign, characterized by preservation of right ventricular wall motion in the basal and apical regions and dyskinesia in the region of the mid right ventricular free wall. This abnormality is highly specific for acute pulmonary embolism and is likely secondary to acute increases in right ventricular load.

Any disease that causes increased pulmonary vascular resistance can lead to right ventricular dilatation and dysfunction. For example, long-standing chronic obstructive pulmonary disease increases pulmonary vascular resistance and results in cor pulmonale. Acute pneumonia can cause findings that are similar to acute pulmonary embolism, and right ventricular dysfunction has been a hallmark of severe COVID-19 disease due to either macro- or microthrombosis in the pulmonary vasculature. In patients with right ventricular dilatation without obvious pulmonary disease, intracardiac shunts should be considered. The increased flow through the pulmonary vasculature resulting from an atrial septal or ventricular septal defect can, over time, result in elevation in pulmonary vascular resistance with subsequent dilatation and hypertrophy of the right ventricle. Right ventricular dilatation and dysfunction can be seen in left-sided heart disease, and patients who develop right ventricular dilatation and dysfunction due to predominantly left-sided disease have worse outcomes.

In addition to assessment of left and right ventricular structure and function, assessment of the other cardiac chambers also provides important clues to intracardiac and systemic diseases. Enlargement of the left atrium is common in patients with hypertension and is also suggestive of increased left ventricular filling pressures; indeed, left atrial size is often termed the “hemoglobin A_{1c}” of diastolic function, because left atrial enlargement reflects long-standing increase in left-sided filling pressures. Right atrial dilatation and dilatation of the inferior vena cava are common in conditions in which central venous pressure is elevated.

PATIENT SAFETY CONSIDERATIONS

■ RADIATION EXPOSURE

Both cardiac CT and radionuclide imaging expose patients to ionizing radiation. Several recent publications have raised concern regarding the potential harmful effects of ionizing radiation associated with cardiac imaging. The *effective dose* is a measure used to estimate the biologic effects of radiation and is expressed in millisieverts (mSv). However, measuring the radiation effective dose associated with diagnostic imaging is complex and imprecise and often results in varying estimates, even among experts. The effective dose from a typical myocardial perfusion SPECT scan ranges between ~4 and 11 mSv, depending on the protocol and type of scanner used. The effective dose from a typical myocardial perfusion PET scan is lower, ~2.0–4 mSv. Radiation exposure associated with cardiac CT is variable and, as with radionuclide imaging, also depends on the imaging protocol and scanner used. Although historic radiation doses with cardiac CT have been quite high, the introduction of newer technologies (e.g., x-ray tube modulation, prospective ECG gating) has resulted in a significant

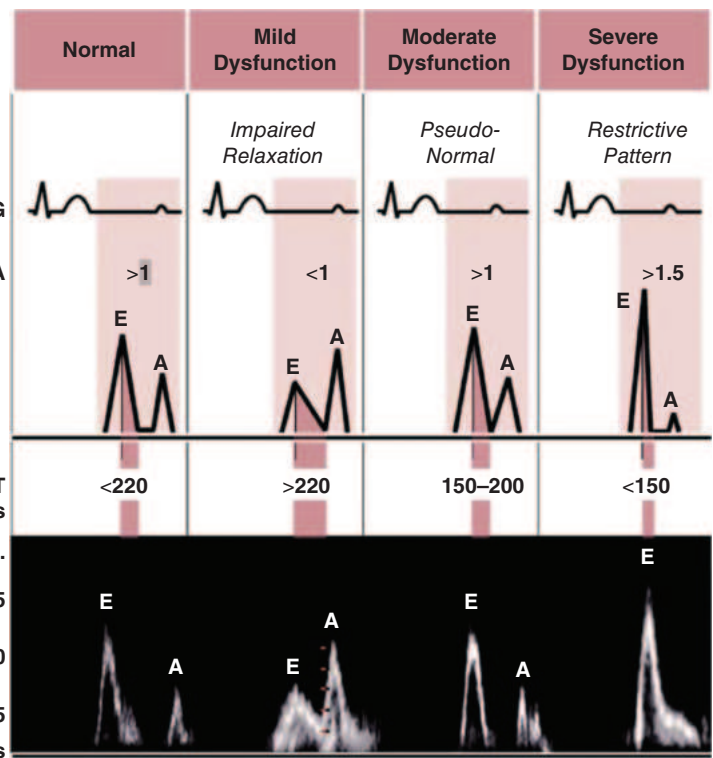


FIGURE 248-8 Mitral inflow Doppler waveforms in diastolic dysfunction. Left ventricle diastolic filling patterns (normal, impaired relaxation, pseudonormal, and restrictive filling). See text for details. ECG, electrocardiogram; LV, left ventricle; PW, pulsed wave. (Modified from CY Ho, BE Bulwer: *Echocardiographic assessment of diastolic function, in Essential Echocardiography. A Practical Handbook with DVD.* CY Ho, BE Bulwer (eds). Totowa, NJ: Humana Press; 2007, p 124.)

dose reduction. The current average radiation dose for a coronary CTA ranges from 3 to 15 mSv and, in selected cases, can be as low as 1 mSv. Imaging laboratories follow the ALARA (as low as reasonably achievable) principle when balancing the clinical need and imaging approach. By comparison, the average dose for invasive coronary angiography is ~7 mSv, whereas exposure to radiation from natural sources in the United States amounts to ~3 mSv annually.

The risk of a fatal malignancy from medical imaging–related radiation is difficult to estimate precisely but is likely small and difficult to discern from the background risk of natural malignancies. The small but potential radiation risks from imaging mandate an assessment of the risk-versus-benefit ratio in the individual patient. In this context, one must also consider the risks of missing important diagnostic information by not performing a test (which could potentially influence near-term management and outcomes) for a theoretical concern of a small long-term risk of malignancy. Before ordering any test, especially one associated with ionizing radiation, we must ensure the appropriateness of the study and that the potential benefits outweigh the risks. The likelihood that the study being considered will affect the patient's clinical management should be addressed before testing is performed. It is also important that “routine” follow-up scans in asymptomatic individuals be avoided.

■ CONTRAST AGENTS

Contrast agents are commonly used in cardiac CT, CMR, and echocardiography. Although their use significantly enhances the diagnostic information of each of these tests, there are also potential risks from the administration of contrast agents that should be considered.

The risk of adverse reactions from iodinated contrast agents used in cardiac CT is well established. The precise pathogenesis of contrast reactions following intravascular administration of iodinated contrast

media is not known. The overall incidence of contrast reactions is 0.4–3% with nonionic formulations and higher for ionic formulations. Most contrast adverse reactions are mild and self-limiting. The risk of contrast-induced nephropathy (CIN) in patients with relatively normal renal function (estimated glomerular filtration rate [eGFR] >60 mL/min) is low. In most patients, CIN is self-limited, and renal function usually returns to baseline within 7–10 days, without progressing to chronic renal failure. However, this risk increases in patients with GFR <60 mL/min, especially older diabetic subjects. In such patients, appropriate screening and pre- and postscan hydration are necessary.

The use of gadolinium-based contrast agents (GBCAs) improves CMR imaging by enhancing myocardial tissue contrast or delineating cardiac or vascular structures. All GBCAs are chelated to render the compounds nontoxic and facilitate renal excretion. Mild reactions from GBCAs, such as skin itchiness or redness, occur in ~1% of patients, but severe or anaphylactic reactions are very rare at approximately one in 200,000 patients. Older generation (group I) linear-structured GBCAs have been associated with a rare but serious condition known as nephrogenic systemic fibrosis (NSF), which is an interstitial inflammatory reaction manifested as fibrosis of tissues or internal organs and even death. Risk factors to developing NSF include high-dose use of group I GBCA in presence of severe renal dysfunction (eGFR <30 mL/min per 1.73 m²), need for hemodialysis, an eGFR <15 mL/min per 1.73 m², acute renal deterioration, and concurrent proinflammatory/systemic illnesses. Newer generation (group II) macrocyclic-structured GBCAs have an excellent safety profile across all patients with chronic kidney dysfunction and indeed are now the standard GBCA of choice in most MRI centers. The American College of Radiology considers using group II agents as safe in patients with severe renal dysfunction or on dialysis. For patients with a clinical indication for MRI, checking the serum eGFR level is no longer recommended before the use of group II GBCA. With the widespread use of group II GBCA, routine pretest screening, and weight-based dosing, a near-zero incidence of NSF has been reported in the past decade.

Contrast agents can also be used in echocardiography. Injected agitated saline is used routinely to assess cardiac shunts, because these “bubbles” are too large to traverse the pulmonary circulation. After saline injection, the presence of bubbles in the left side of the heart is indicative of shunt, although the location can sometimes be difficult to determine. The current U.S. Food and Drug Administration (FDA)-approved use of echocardiographic contrast agents is for opacification of left-sided chambers and to improve delineation of left ventricular endocardial border in patients with suboptimal echocardiograms. These agents are either albumin- or lipid-based microspheres filled with inert gases, typically perfluorocarbons. They are considered extremely safe, although they have, in extremely rare instances, been associated with allergic reactions and neurologic events.

■ SAFETY CONSIDERATIONS OF CMR IN PATIENTS WITH PACEMAKERS AND DEFIBRILLATORS

There are now numerous FDA-approved MRI-conditional internal cardiac defibrillators and pacemakers that are safe to undergo an MRI

study up to 3T, under well-defined scanning conditions in experienced centers. For non-FDA-approved cardiac devices (legacy devices), collective evidence has also indicated that MRI studies can be safely performed at 1.5T under normal operational settings, in absence of fractured, epicardial, or abandoned leads, and when an experienced staff is available to interrogate the cardiac device before and after MRI study. The Centers for Medicare and Medicaid Services have approved and expanded coverage of MRI studies in patients with an implanted legacy device since April 2018.

PATIENT-CENTERED APPLICATIONS OF CARDIAC IMAGING

■ CORONARY ARTERY DISEASE

The basis for the diagnostic application of imaging tests in patients with known or suspected CAD should be viewed considering the pretest probability of disease as well as the specific characteristics of imaging tests (i.e., sensitivity and specificity). In symptomatic patients, the prevalence or pretest probability of CAD differs based on the type of symptom (typical angina, atypical angina, noncardiac chest pain), as well as on age, gender, and coronary risk factors. In an individual patient, the results of the initial test inform the posttest likelihood of CAD. In patients undergoing sequential testing (e.g., ECG treadmill testing followed by stress imaging), the posttest probability of disease after the first test becomes the pretest likelihood of disease for the second test. Regardless of the sequence, the expectation is that a test will provide sufficient information to confirm or exclude the diagnosis of CAD and that such information will allow accurate risk stratification to be able to guide management decisions.

Table 248-3 summarizes the relative diagnostic accuracies of cardiac imaging modalities for the diagnosis of CAD.

It is important to highlight that most studies included in meta-analyses of the diagnostic accuracy of cardiac imaging modalities for the diagnosis of CAD were retrospective, small, single-center studies, comprising predominantly male patients with a high prevalence of CAD (>50–60%). Multicenter studies assessing the performance of individual modalities or comparing different modalities have consistently resulted in more modest diagnostic accuracies, tracking more closely with how these tests perform in clinical practice.

Stress Echocardiography The hallmark of myocardial ischemia during stress echocardiography is the development of new regional wall motion abnormalities and reduced systolic wall thickening (**Video 248-3**). Stress echocardiography can be performed in conjunction with exercise or dobutamine stress. Stress echocardiography is best at identifying inducible wall motion abnormalities in previously normally contracting segments. In a patient with wall motion abnormalities at rest, the specificity of stress echocardiography is reduced, and worsening regional function of a previously abnormal segment might reflect worsening contractile function in the setting of increased wall stress rather than new evidence of inducible ischemia.

The advantages of stress echocardiography over other stress imaging techniques include its relatively good diagnostic accuracy, widespread

TABLE 248-3 Comparative Diagnostic Accuracy of Cardiac Imaging Approaches to Coronary Artery Disease

IMAGING MODALITY	PUBLISHED DATA	SENSITIVITY	SPECIFICITY
Exercise echocardiography	15 studies (n = 1849 patients)	84%	82%
Dobutamine echocardiography	28 studies (n = 2246 patients)	80%	84%
SPECT MPI	113 studies (n = 11,212 patients)	88%	76%
Myocardial perfusion PET	9 studies (n = 650 patients)	93%	81%
CMR perfusion	37 studies (n = 2841 patients)	91%	81%
CMR wall motion	14 studies (n = 754 patients)	83%	86%
Coronary CTA	18 studies (n = 1286 patients)	99%	89%

Note: In these studies, the diagnosis of coronary artery disease was based on the presence of a >50% or >70% stenosis on invasive coronary angiography.

Abbreviations: CMR, cardiac magnetic resonance; CTA, computed tomography angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

availability, no use of ionizing radiation, and relatively low cost. Limitations of stress echocardiography include (1) the technical challenges associated with image acquisition at peak exercise because of exertional hyperpnea and cardiac excursion, (2) the fact that rapid recovery of wall motion abnormalities can be seen with mild ischemia (especially with one-vessel disease, which limits sensitivity), (3) difficulty detecting residual ischemia within an infarcted territory because of resting wall motion abnormality, (4) high operator dependence for acquisition of echocardiographic data and analysis of images, and (5) the fact that good-quality complete images viewing all myocardial segments occurs in only 85% of patients. Newer techniques including second harmonic imaging and the use of intravenous contrast agents improve image quality, but their effect on diagnostic accuracy has not been well documented.

As with nuclear perfusion imaging, stress echocardiography is often used for risk stratification in patients with suspected or known CAD. A negative stress echocardiogram is associated with an excellent prognosis, allowing identification of patients at low risk. Conversely, the risk of adverse events increases with the extent and severity of wall motion abnormalities on stress echocardiography.

Stress Radionuclide Imaging SPECT myocardial perfusion imaging is the most common form of stress imaging tests for CAD evaluation. The presence of a reversible myocardial perfusion defect is indicative of ischemia (Fig. 248-9, left panel), whereas a fixed perfusion defect generally reflects prior myocardial infarction (Fig. 248-9, right panel). As discussed above, PET has advantages compared to SPECT, but it is not widely available and is more expensive and, thus, considered an emerging technology in clinical practice.

Nuclear perfusion imaging is another robust approach to diagnose obstructive CAD, quantify the magnitude of inducible myocardial ischemia, assess the extent of tissue viability, and guide therapeutic management (i.e., selection of patients for revascularization). One of the most valuable clinical applications of radionuclide perfusion imaging is for risk stratification. It is well established that patients with a normal SPECT or PET study exhibit a low rate of major adverse cardiac events of <1% annually. Importantly, the risks of death and myocardial infarction increase linearly with increasing magnitude of perfusion abnormalities, reflecting the extent and severity of CAD.

Despite the widespread use and clinical acceptance of radionuclide imaging in CAD evaluation, a recognized limitation of this approach is that it often uncovers only coronary territories supplied by the most

severe stenoses. Consequently, it is relatively insensitive to accurately delineate the extent of obstructive angiographic CAD, especially in the setting of multivessel disease. The use of quantitative myocardial blood flow and coronary flow reserve with PET can help mitigate this limitation. In patients with so-called “balanced” ischemia or diffuse CAD, measurements of coronary flow reserve uncover areas of myocardium at risk that would generally be missed by performing only relative assessments of myocardial perfusion (Fig. 248-10). Conversely, a normal coronary flow reserve is associated with a very high negative predictive value for excluding high-risk angiographic CAD. These measurements of coronary flow reserve also contribute to risk stratification across the spectrum of ischemic changes, including patients with visually normal myocardial perfusion.

HYBRID CT AND NUCLEAR PERFUSION IMAGING Because many of the newer generation nuclear medicine scanners integrate CT and a gamma camera in the same acquisition gantry, it is now possible to acquire and quantify myocardial scar and ischemia and CAC scoring from a single dual-modality study (SPECT/CT or PET/CT) (Fig. 248-11). The rationale for this integrated approach is predicated on the fact that the perfusion imaging approach is designed to uncover only obstructive atherosclerosis. Conversely, CAC scoring provides a quantitative measure of the anatomic extent of atherosclerosis. This provides an opportunity to improve the conventional models for risk assessment using nuclear imaging alone, especially in patients without known CAD.

Cardiac CT Voluminous plaques are more prone to calcification, and stenotic lesions frequently contain large amounts of calcium. Indeed, there is evidence that high CAC scores are generally predictive of a higher likelihood of obstructive CAD, and the available data support the concept of a threshold phenomenon governing this relationship (i.e., Agatston score >400). However, given the fact that CAC scores are not specific markers of obstructive CAD, one should be cautious in using this information as the basis for referral of patients to coronary angiography, especially in symptomatic patients with low-risk stress tests. Conversely, CAC scores <400, especially in symptomatic patients with intermediate-high likelihood of CAD, as in those with typical angina, may be less effective in excluding CAD, especially in young symptomatic men and women who may have primarily noncalcified atherosclerosis (Fig. 248-12).

As discussed above, the improved temporal and spatial resolution of modern multidetector CT scanners offers a unique non-invasive approach to delineate the extent and severity of coronary

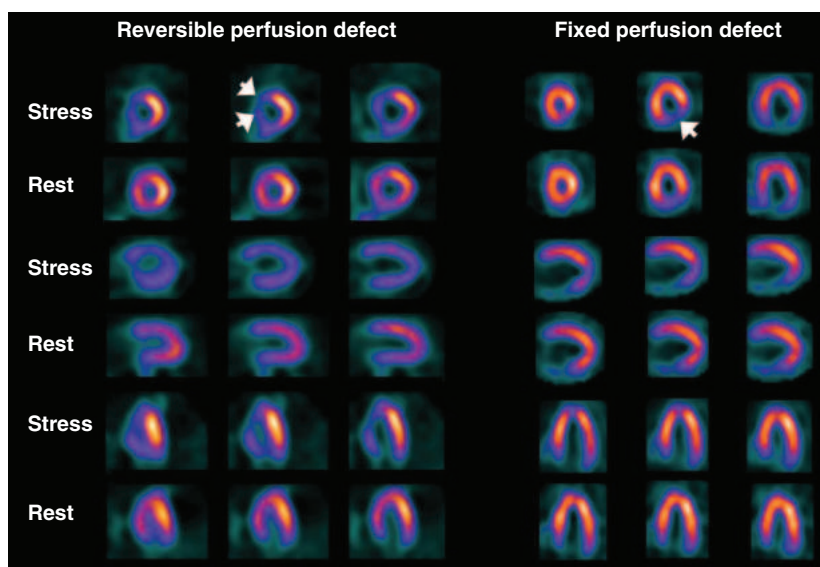


FIGURE 248-9 Selected technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography images of two different patients demonstrating a reversible perfusion defect involving the anterior and septal left ventricular wall, reflecting ischemia in the left anterior descending coronary territory (arrows in left panel), and a fixed perfusion defect involving the inferior and inferolateral walls consistent with myocardial scar in the right coronary territory (arrow in right panel).

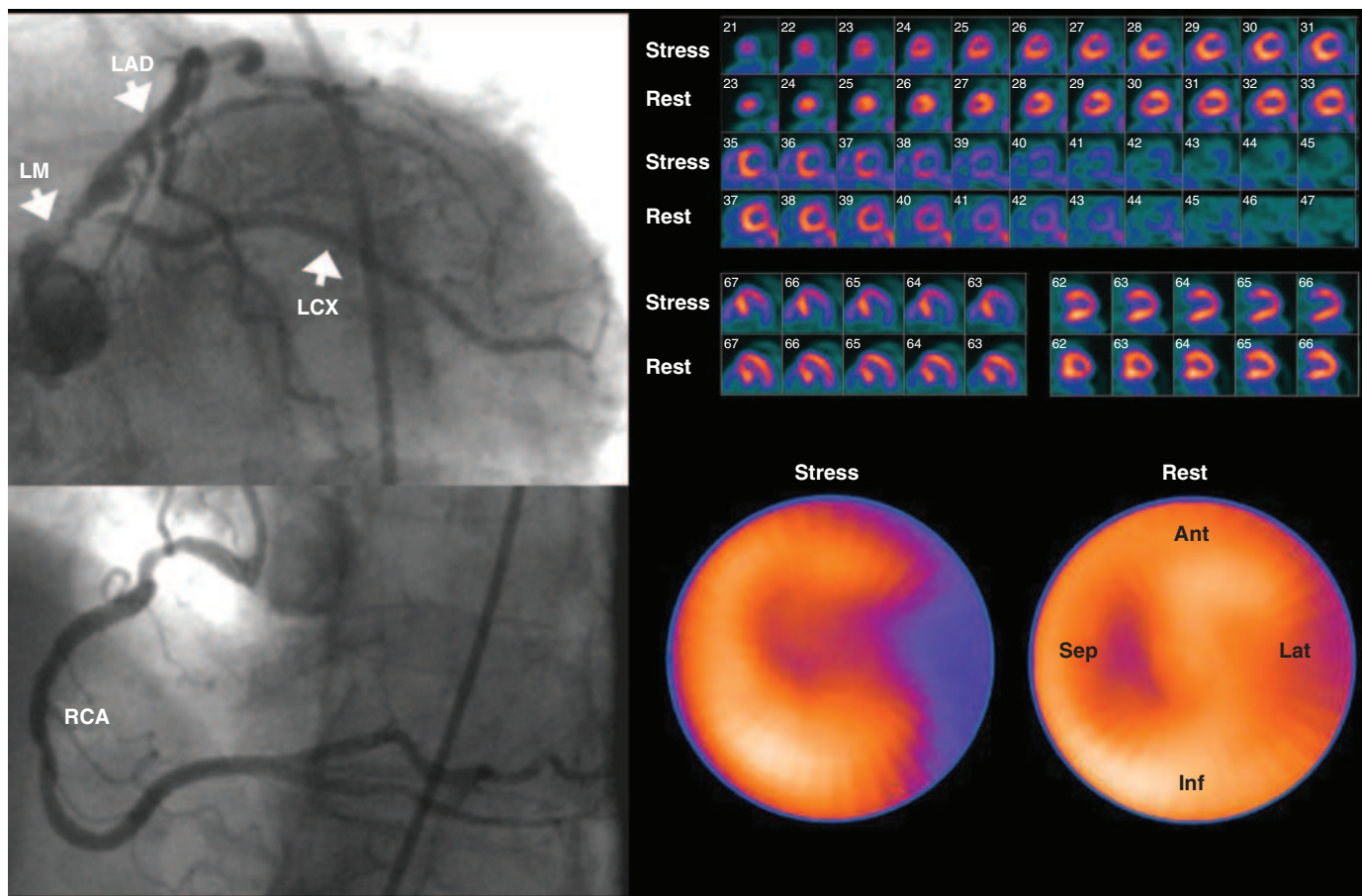


FIGURE 248-10 Coronary angiographic (*left panel*) and rubidium-82 myocardial perfusion positron emission tomography images (*right panel*) in an 85-year-old female with diabetes presenting with chest pain. The coronary angiogram demonstrates significant stenoses of the left main and circumflex coronary arteries. However, the perfusion images demonstrate only a reversible lateral wall defect. Quantification of stress and rest myocardial blood flow demonstrated a significant, global reduction on coronary flow reserve (estimated at 1.2, normal value >2.0), reflecting extensive myocardium risk that was underestimated by the semiquantitative estimates of myocardial perfusion. LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; RCA, right coronary artery.

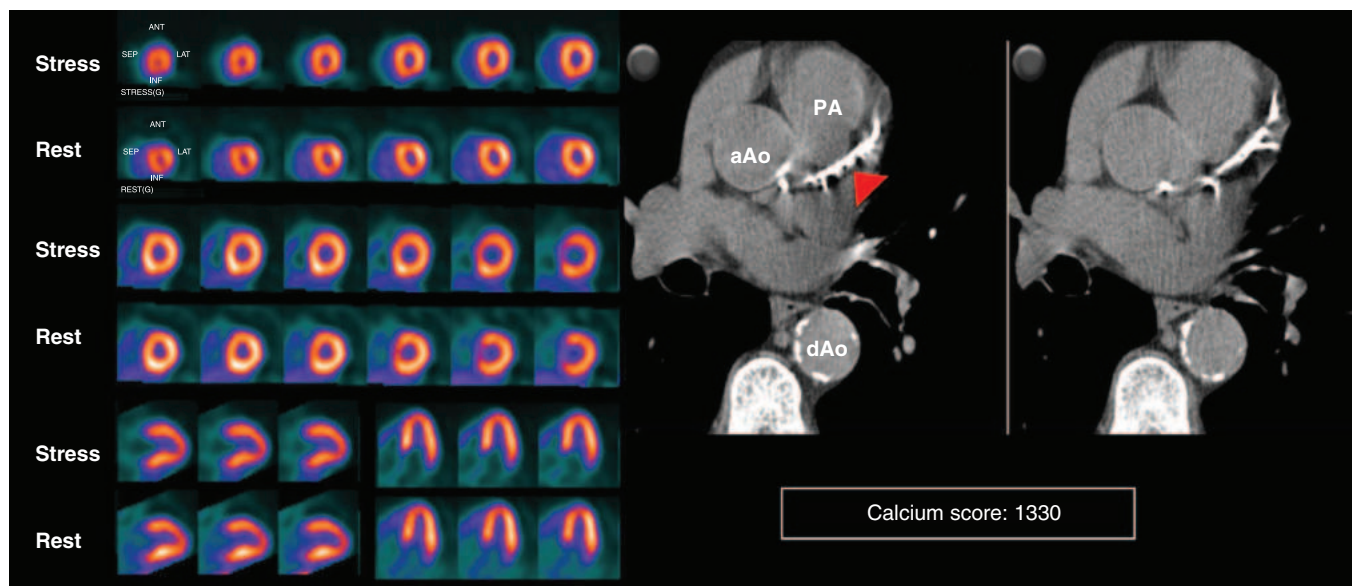


FIGURE 248-11 Stress and rest rubidium-82 myocardial perfusion positron emission tomography (PET) images (*left*) and noncontrast gated computed tomography (CT) images (*right*) delineating the extent and severity of coronary artery calcifications obtained with integrated PET/CT imaging. The images demonstrate extensive atherosclerosis (Agatston coronary calcium score = 1330) without flow-limiting disease based on the normal perfusion study. aAo, ascending aorta; dAo, descending aorta; PA, pulmonary artery.

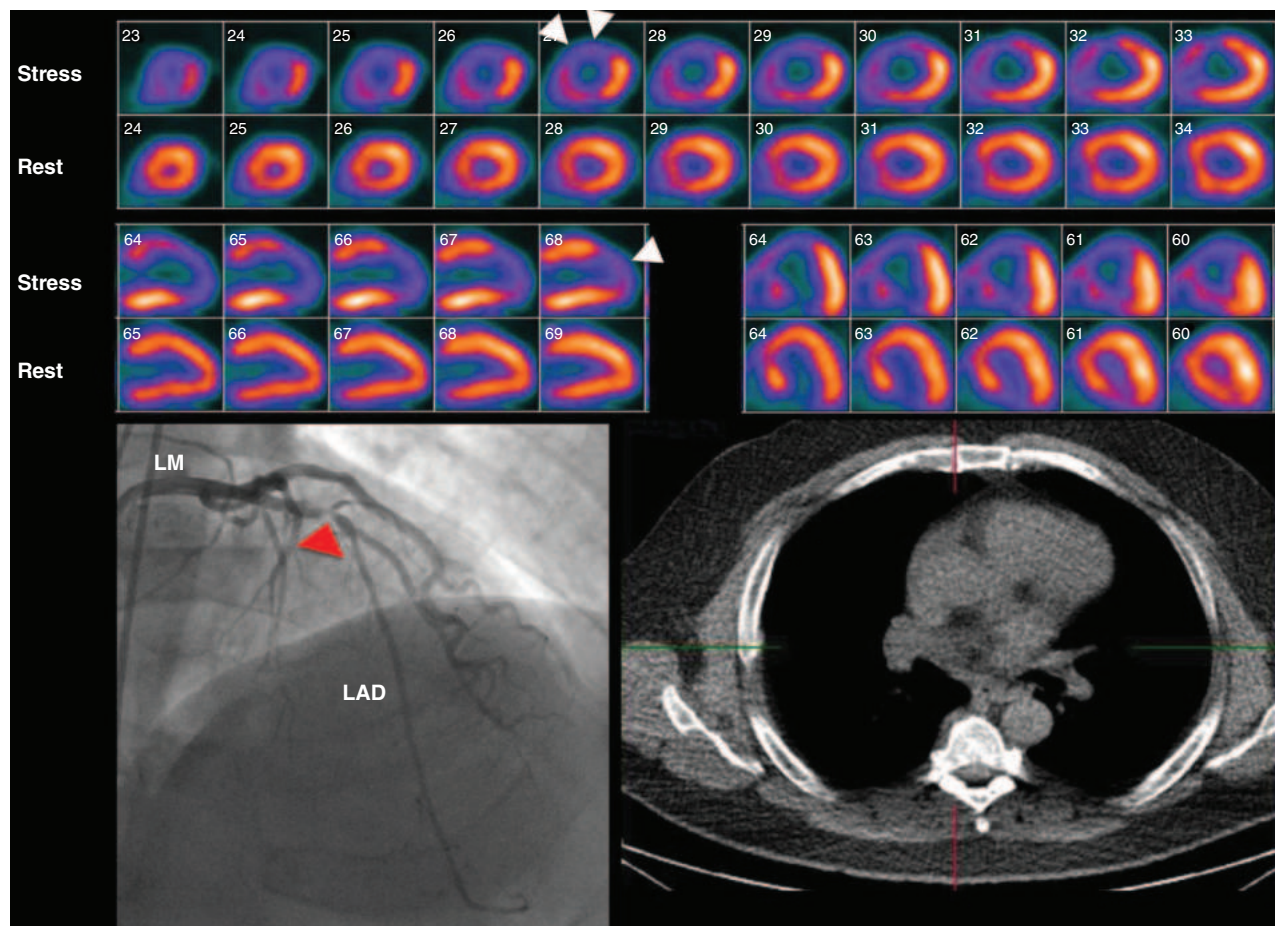


FIGURE 248-12 Stress and rest rubidium-82 myocardial perfusion positron emission tomography images (*top*), noncontrast gated computed tomography images (*lower right*), and selected coronary angiographic images obtained on a 59-year-old male patient with atypical angina. Despite the absence of significant coronary calcifications (Agatston calcium score = 0), the perfusion images demonstrated a dense and reversible perfusion defect involving the anterior and anteroseptal walls (*arrows*), reflecting significant obstructive disease in the left anterior descending coronary artery (LAD), confirmed on angiography. LM, left main artery.

atherosclerosis with coronary CTA. The extremely high sensitivity of this approach offers a very effective means for excluding the presence of CAD (high negative predictive value) (Table 248-3). In the setting of high coronary calcium scores (e.g., >400), however, specificity is reduced because the blooming artifact of calcium does not allow one to evaluate the vessel lumen accurately. Given the high negative predictive value of CTA, a normal scan result effectively excludes obstructive CAD and abolishes the need for further investigation. As discussed below, this may be quite useful in patients with low-intermediate clinical risk presenting to the emergency room for chest pain. However, the limited capability of this technique to determine which coronary plaques are flow limiting can make abnormal scan results more difficult to interpret, especially in terms of the possible need of revascularization. There are emerging data suggesting that by adding a stress myocardial perfusion CT evaluation (similar to stress perfusion CMR) (*Fig. 248-13, top panel*) or an estimated fractional flow reserve (so-called FFR_{CT}) (*Fig. 248-13, lower panel*), one can define the hemodynamic significance of anatomic stenosis. FFR_{CT} is beginning to enter routine clinical practice. However, CT myocardial perfusion remains an emerging technology.

As with invasive coronary angiography, assessments of the extent of CAD by CTA can also provide useful prognostic information. A low 1-year cardiac event rate has been reported for patients without coronary atherosclerosis on CTA. For patients with obstructive CAD, the risk of adverse cardiac events increases proportionally with the extent of angiographically obstructive CAD. There is new evidence that even the presence of nonobstructive atherosclerosis increases the risk of adverse cardiac events.

Although CTA can be helpful in assessing patency of bypass grafts, the assessment of stents is somewhat more challenging because the limited spatial resolution of CT and stent diameter (<3 mm being

associated with the highest number of partial lumen visualization and nondiagnostic scans) both contribute to limited clinical results.

CMR Imaging CMR evaluates for ischemia from CAD by assessing regional myocardial perfusion or regional wall motion at rest and during pharmacologic stress with an intravenous infusion of vasodilator agent or dobutamine. Myocardial perfusion is evaluated by injecting a GBCA bolus followed by imaging data acquisition as the contrast passes through the cardiac chambers and into the myocardium. Relative perfusion deficits are recognized as regions of low signal intensity (black) within the myocardium (*Video 248-4*). Several minutes after GBCA injection, LGE imaging allows detection of bright areas of myocardial scar (white), which permits comparison of regions of hypoperfusion and infarction to quantify myocardial ischemia (*Fig. 248-14*).

With better delineation of the endocardial borders, dobutamine CMR has better diagnostic accuracy than dobutamine echocardiography for detection of CAD, especially in patients with poor acoustic window (Table 248-3). High-dose dobutamine carries the risk of serious ventricular arrhythmias (~1%), but most cases can be prevented with proper monitoring of vital signs and regional cine function. The advantages of stress perfusion CMR over SPECT include its higher spatial resolution, which allows detection of subendocardial ischemia or infarction that may be missed by SPECT. As with other imaging modalities, stress CMR studies also provides robust risk stratification in practice. In a recent randomized controlled trial, a stress CMR-guided strategy was shown to improve the guidance toward the use of invasive investigation and coronary revascularization.

Selecting a Testing Strategy in Patients without Known CAD

As discussed above, there are many options for the evaluation of a patient with suspected CAD presenting with chest pain symptoms. The critical questions to be answered by a testing strategy include the

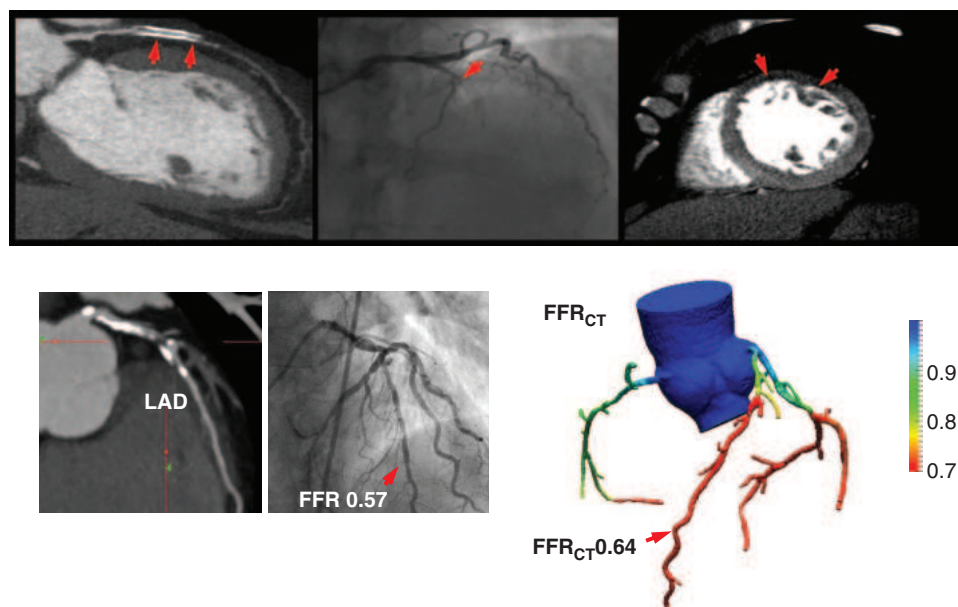


FIGURE 248-13 Examples of novel approaches to the assessment of flow-limiting coronary artery disease (CAD) with cardiac computed tomography (CT). In the *top panel*, representative views of a coronary CT angiogram (CTA; *left*), coronary angiogram (*middle*), and stress myocardial perfusion CT (*right*) images in a patient with CAD and prior stenting of the left anterior descending coronary artery (LAD) are presented. On the CTA, the stent (*arrows*) is totally occluded as evidenced by the loss of contrast enhancement distal to the stent. The coronary angiogram demonstrates a concordant total occlusion of the LAD. On the perfusion CT images, there is a black rim (*arrows*) involving the anterior and anterolateral walls, indicating the lack of contrast opacification during stress consistent with myocardial ischemia. (*Images courtesy of CORE 320 investigators.*) The *lower panel* illustrates an example of fractional flow reserve (FFR) estimates with coronary CTA (*left*) compared to the reference standard of invasive FFR. The FFR reflects the pressure differential between a coronary segment distal to a stenosis and the aorta. In normal coronary arteries, there is no gradient, and FFR is 1. An FFR <0.80 is consistent with a hemodynamically significant stenosis. (*Images courtesy of Dr. James Min, Cornell University, New York.*)

following: (1) Does the chest pain reflect obstructive CAD? (2) What are the short- and long-term risks? (3) Does the patient need to be considered for revascularization? Large-scale clinical trials have demonstrated the benefits of guideline-directed medical therapies where the majority of the patients with stable CAD are at low risk of serious cardiac events on guideline-directed medical therapy alone, and coronary revascularization is best reserved for patients with severe symptoms

despite adequate medical therapy. However, imaging will continue to play a significant role in diagnosing the etiology of chest pain and risk assessment of individual patients.

For symptomatic patients without a prior history of CAD, the 2021 American College of Cardiology/American Heart Association chest pain guidelines assigned a class I recommendation for stress imaging testing and coronary CTA. Most common stress imaging strategies include stress echocardiography and radionuclide imaging. However, CMR and PET have both been shown to have higher test accuracy than SPECT. In patients with intermediate clinical risk, stress imaging with either SPECT or echocardiography has been shown to reclassify patients accurately who are initially classified as intermediate risk by exercise treadmill testing (ETT) as low or high risk. ETT as the initial testing strategy is still valuable for patients with a normal or nearly normal resting ECG who can exercise.

The use of exercise testing in women presents difficulties that are not seen in men, reflecting the differences in the lower prevalence of obstructive CAD in women and the different accuracy of exercise testing in men and women. Compared with men, the lower pretest probability of disease in women means that more test results are false positive. In some of these patients, a positive ETT may reflect true myocardial ischemia caused by microvascular coronary artery dysfunction (so-called *microvascular disease*). In addition, the inability of many women to exercise to maximum aerobic capacity, the greater prevalence of mitral valve prolapse and microvascular disease, and possibly other reasons may contribute to the differences with men as well. The difficulties of using exercise testing for diagnosing obstructive CAD in women have led to speculation that stress imaging may be preferred over standard stress testing. However, recent data from the WOMEN study suggest that in symptomatic, low-risk women who can exercise, standard ETT is a very effective initial diagnostic strategy as compared to stress radionuclide imaging. Indeed, the 2-year outcomes were similar in both diagnostic strategies, and the ETT-first approach resulted in 48% lower costs compared to exercise radionuclide imaging.

An imaging strategy is the recommended first step for patients who are unable to exercise to an adequate workload and/or those with abnormal resting ECGs (e.g., left ventricular hypertrophy with strain, left bundle branch block). Importantly, the most recent documents regarding appropriate use of imaging also considered that an imaging

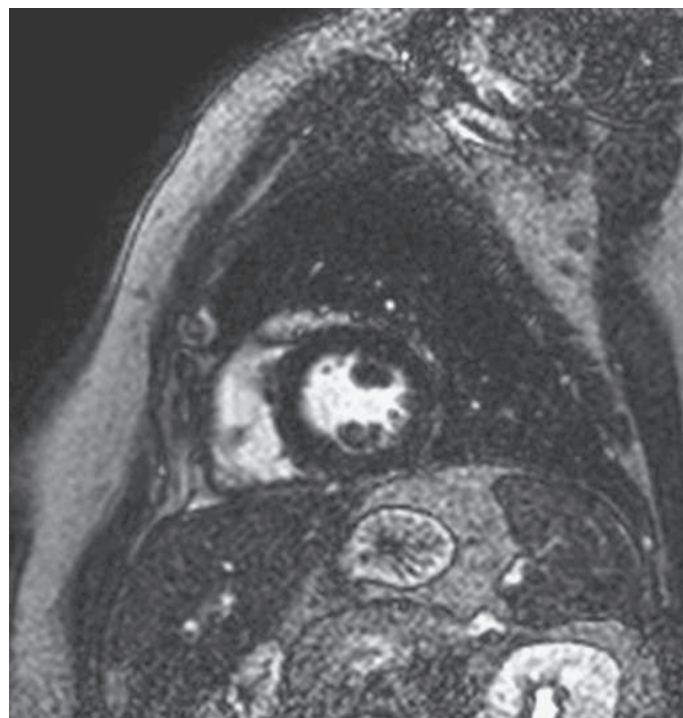


FIGURE 248-14 The image shows the late gadolinium enhancement image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

strategy may be an appropriate first step in patients with intermediate-high likelihood of CAD (e.g., diabetics, renal impairment) due to increased overall sensitivity for diagnosis of CAD and improved risk stratification. In considering an imaging strategy, the evidence supporting the role of ischemia assessment versus anatomy must be considered. From the discussion above, for patients with atypical chest pain and a low-pretest risk of CAD, a normal coronary CTA is helpful because it effectively excludes the presence of obstructive CAD and the need for further testing, defines a low clinical risk, and makes management decisions regarding referral to coronary angiography straightforward. However, in patients with an intermediate or higher pretest risk, coronary CTA is less effective in excluding obstructive CAD because of its limited accuracy to define stenosis severity and predict ischemia; however, abnormal CTA results are more problematic to interpret and to use as the basis for defining the potential need of invasive coronary angiography and revascularization. In such patients, a follow-up stress test is usually required to determine the possible need of revascularization (Fig. 248-15).

The justification of stress imaging in testing strategies has hinged on the identification of which patients may benefit from a revascularization strategy by means of non-invasive estimates of jeopardized myocardium rather than angiography-derived anatomic stenoses. However, recent evidence from the ISCHEMIA trial suggests that optimal medical therapy provides comparable prognostic benefit to an early invasive strategy in patients with moderate or severe myocardial ischemia. Coronary revascularization is reserved for patients with very extensive evidence of ischemia by stress imaging and/or inadequate symptom control by optimal medical therapy. While the available data suggest similar diagnostic accuracy for SPECT and echocardiography but higher accuracy for PET and CMR, the choice of strategy depends on availability and local expertise.

Selecting a Testing Strategy in Patients with Known CAD

Use and selection of testing strategies in symptomatic patients with established CAD (i.e., prior angiography, prior myocardial infarction, prior revascularization) differ from those in patients without prior CAD. Although standard ETT may help distinguish cardiac from noncardiac chest pain, exercise ECG has several limitations following myocardial infarction and revascularization (especially coronary artery bypass grafting). These patients frequently have rest ECG abnormalities. In addition, there is a clinical need to document both the magnitude and localization of ischemia to be able to direct therapy, especially the potential need for targeted revascularization. Consequently, imaging tests are preferred for evaluating patients with known CAD.

There are also important differences in the effectiveness of imaging tests in these patients. As discussed above, coronary CTA is limited in patients with prior revascularization. While CTA provides excellent visualization of the bypass grafts, the native circulation tends to get heavily calcified and is generally not a good target for imaging with CTA. Likewise, blooming artifacts from metallic stents also limit the application of coronary CTA in patients with prior percutaneous coronary intervention. If an anatomic strategy is indicated, direct referral to invasive angiography is preferred.

Stress imaging approaches are especially useful and preferred in symptomatic patients with established CAD. As in patients without prior CAD, normal imaging studies in symptomatic patients with established CAD also identify a low-risk cohort. In those with abnormal stress imaging studies, the degree of abnormality relates to posttest risk. In addition, stress imaging approaches can localize and quantify the magnitude of ischemia, thereby assisting in planning targeted revascularization procedures. As in patients without prior CAD, the

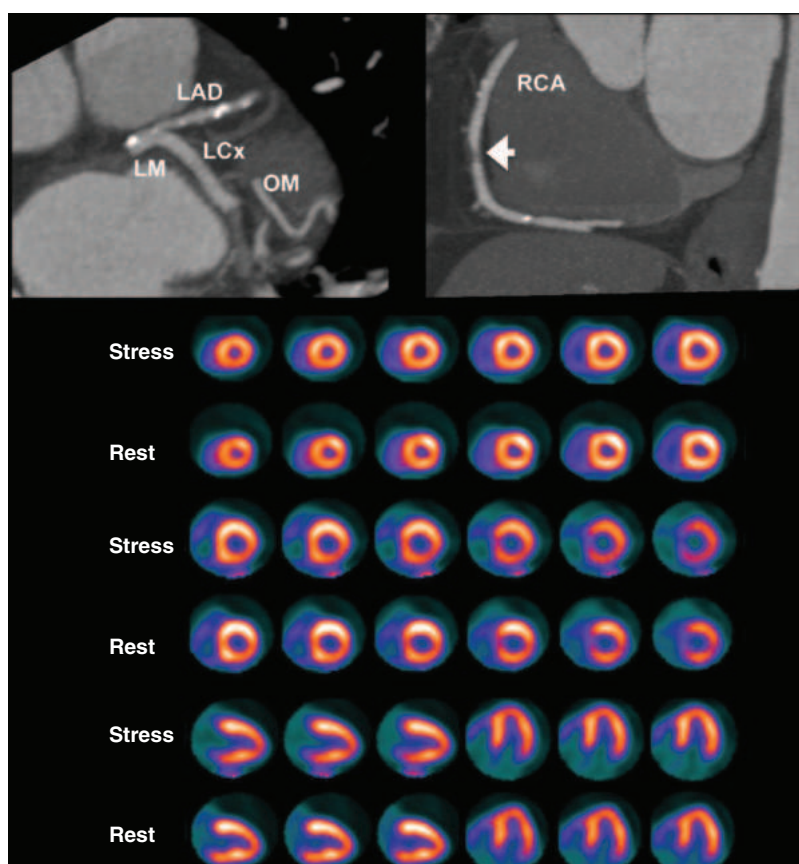


FIGURE 248-15 Selected views from coronary computed tomography angiographic (CTA) images (top panel) and stress and rest rubidium-82 myocardial perfusion positron emission tomography images (lower panel) obtained on a 64-year-old male patient with atypical angina. The CTA images demonstrate dense focal calcifications in the left main (LM) and left anterior descending (LAD) coronary arteries and a significant noncalcified plaque in the mid right coronary artery (RCA; arrow). The myocardial perfusion images demonstrated no evidence of flow-limiting stenosis. LCx, left circumflex artery; OM, obtuse marginal branch.

choice of stress imaging strategy depends on availability and local expertise.

Testing Strategy Considerations in Patients Presenting with Chest Pain to the Emergency Department

Although acute chest pain is a frequent reason for patient visits to the emergency department (ED), only a small minority of those presentations represent an acute coronary syndrome (ACS). Strategies used in the evaluation of these patients include novel cardiac biomarkers (e.g., serum troponins), conventional stress testing (ETT), and noninvasive cardiac imaging. It is generally accepted that the primary goal of this evaluation is exclusion of ACS and other serious conditions rather than detection of CAD.

The routine evaluation of acute chest pain in most centers in the United States includes admission to a chest pain unit to rule out ACS with the use of serial ECGs and cardiac biomarkers. In selected patients, stress testing with or without imaging may be used for further risk stratification. Stress echocardiography and radionuclide imaging are among the most frequently used imaging approaches in these patients. Multiparametric CMR imaging has also been used successfully in patients with acute chest pain (Video 248-5). Due to its ability to probe multiple aspects of myocardial physiology, cardiac anatomy, and tissue characterization with LGE imaging, CMR is useful in diagnosing conditions that mimic ACS (e.g., acute myocarditis, takotsubo cardiomyopathy, pericarditis) (Fig. 248-16).

As discussed above, coronary CTA is a rapid and accurate imaging technique to exclude the presence of CAD and is well suited for the evaluation of patients with acute chest pain (Fig. 248-17). Four randomized clinical trials have demonstrated the feasibility, safety, and accuracy of coronary CTA in the ED as compared to usual care (which typically includes stress imaging). Patients in these trials had a very low clinical

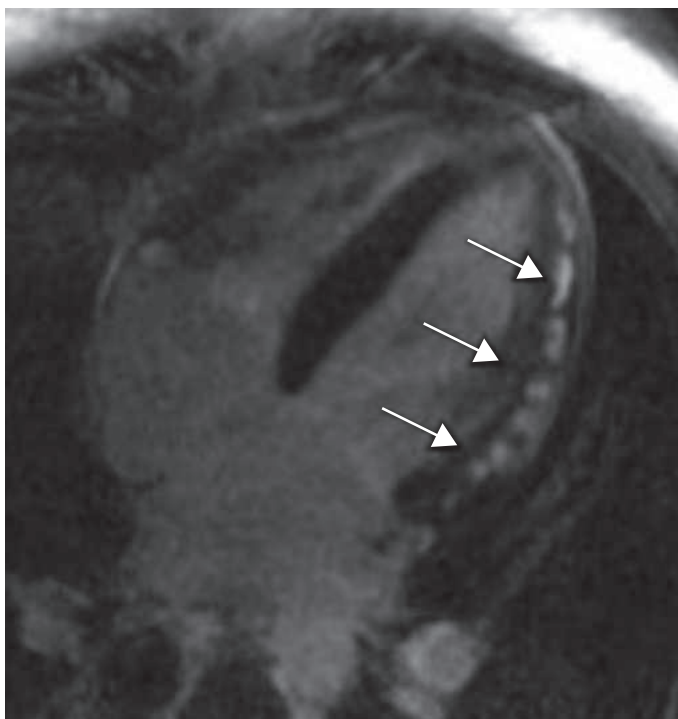


FIGURE 248-16 A four-chamber long-axis late gadolinium enhancement (LGE) image of a patient with acute myocarditis. Note that the LGE primarily involved the epicardial aspect of the myocardium (arrows), sparing the endocardium, which is a feature that distinguishes myocarditis from myocardial infarction, which affects the endocardium. Also note the multiple foci of LGE in this case affecting the lateral wall of the left ventricle. Viral myocarditis often presents with this pattern.

risk. Overall, there were no deaths and very few myocardial infarctions without differences between the groups. Likewise, there were no differences in postdischarge ED visits or rehospitalizations. These studies showed decreased length of stay with coronary CTA, and most but not all reported cost savings. An observation from a recent meta-analysis was that, compared to usual care, more patients assigned to coronary CTA underwent cardiac catheterization (6.3 vs 8.4%, respectively) and revascularization (2.6 vs 4.6%, respectively). The relative increased frequency in the referral to cardiac catheterization and revascularization after coronary CTA compared to stress imaging testing strategies has also been observed in patients with stable chest pain syndromes.

Taken together, the available data clearly suggest that not all patients presenting with acute chest pain require specialized imaging testing. Patients with very low clinical risk and negative biomarkers (especially high-sensitivity troponin assays) can be safely triaged. The use of imaging tests in patients with low-intermediate risk should be carefully considered, especially given the trade-offs discussed above.

VALVULAR HEART DISEASE

Abnormalities of any of the four valvular structures in the heart can lead to significant cardiac dysfunction, heart failure, or even death. Echocardiography, CMR, and cardiac CT can be used for the evaluation of valvular heart disease, although echocardiography is generally considered the first imaging test for the assessment of valvular heart disease. In addition, echocardiography is the most cost-effective screening method for valvular heart disease. In some cases, CMR can complement echocardiography when echocardiographic acoustic window is inadequate, by quantifying blood flow data more precisely or providing complimentary assessment of adjacent vascular structures relevant to the valvular condition.

Echocardiography can be used to assess both regurgitant and stenotic lesions of any of the cardiac valves. Typical indications for echocardiography to assess valvular heart disease include cardiac murmurs identified on physical examination, symptoms of breathlessness that may represent valvular heart disease, syncope or presyncope, and preoperative exams in patients undergoing bypass surgery. A standard echocardiographic examination should include qualitative and quantitative assessment of all valves regardless of indication and should serve as an adequate screening test for significant valvular disease.

Assessment of Aortic Stenosis Aortic stenosis, one of the most common forms of valvular heart disease, most often occurs because of gradual progression of valvular calcification in both normal and congenitally abnormal valves. Assessment of aortic stenosis is most commonly performed with echocardiography, although techniques for quantitative assessment of aortic stenosis with CMR have been developed and increasingly used over the past decade. Echocardiographic assessment generally begins with visual inspection of the valve. This allows for assessment of valvular morphology, whether it is tricuspid, bicuspid, or some variant; degree of leaflet calcification; and leaflet excursion.

The normal aortic valve consists of three leaflets or cusps: the right coronary, the left coronary, and the noncoronary cusps. Abnormalities of cusp development are some of the most common congenital heart anomalies, the most common of which is bicuspid aortic valve, with two opening leaflets rather than three (Fig. 248-18). The aortic valve can be visualized on echocardiography, although sometimes it can be difficult to distinguish true bicuspid aortic valve from variants, including the presence of a vestigial commissure (raphe). Bicuspid aortic valve, one of the most common congenital anomalies, predisposes to both aortic stenosis and aortic insufficiency.

The degree of aortic stenosis is assessed by estimating both the pressure gradient across the valve and the valve area. Patients with moderate aortic stenosis or higher generally have peak instantaneous velocities of 3.0 m/s and higher, and often higher than 4.0 m/s, corresponding to pressure gradients of 36 and 64 mmHg, respectively. Because pressure gradients across the aortic valve can be underestimated in patients with severe left ventricular dysfunction, estimation of

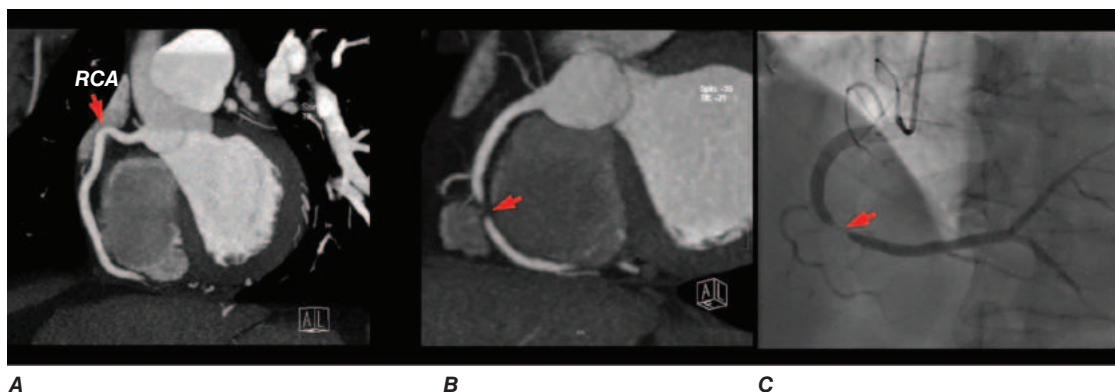


FIGURE 248-17 Representative coronary computed tomography angiographic (CTA) images of two patients presenting to the emergency department with chest pain and negative biomarkers. The patient in **A** had angiographically normal coronary arteries; the panel shows a representative view of the right coronary artery (RCA). **B** and **C** show a corresponding significant stenosis in the mid portion of the RCA on both the CTA (**B**) and invasive angiographic view (**C**). (Images used with permission from Dr. Quynh Truong, Massachusetts General Hospital, Boston, MA.)



FIGURE 248-18 Normal aortic valve in the parasternal long-axis view (**A**) and short-axis view (**B**), and bicuspid aortic valve showing typical 10 o'clock to 4 o'clock leaflet orientation (**C**).

valve area by the continuity principle is the most accurate technique for assessing the severity of the stenosis. However, evaluation of the patient with so-called low-flow or low-gradient aortic stenosis can be challenging and sometimes require provocative testing such as dobutamine echocardiography. In these cases, it is important to distinguish whether the valve is indeed capable of opening further or simply behaving like a stenotic valve because of the low-pressure gradient.

Aortic valve areas $<1.0 \text{ cm}^2$ are generally considered severe, and valve areas $<0.6 \text{ cm}^2$ are considered critical. Because patients with good left ventricular function can often tolerate severe aortic stenosis for a considerable period of time, valve areas or gradients alone should not be used to determine whether an individual patient should undergo aortic valve surgery, as this remains a clinical decision.

Some patients with apparent aortic stenosis have subvalvular or even supravalvular obstruction. Hypertrophic cardiomyopathy represents the classic form of subvalvular aortic stenosis, but this is usually easily distinguished from aortic stenosis on echocardiography as the valve leaflets can be seen opening during systole. Subaortic membranes can behave very similarly to leaflet aortic stenosis, and the membranes themselves can be very thin and difficult to visualize, although the presence of a murmur, a gradient across the valve with aortic leaflets that appear to open normally, is highly suggestive of a membrane. Supravalvular aortic stenosis, although exceedingly rare, also occurs.

The emergence of transcatheter aortic valve intervention as a therapeutic option for patients with severe aortic stenosis who are not optimal candidates for surgical replacement has resulted in a very important clinical role for multimodality imaging. Imaging plays a critical role in preprocedural planning, intraprocedural implantation optimization, and follow-up of these patients. CT plays an important role in defining the eligibility of the proposed access site (CTA of the aorta and iliac arteries) and in defining the anatomic relationships between the aortic valve and aortic root, left ventricle, and coronary ostia. Cardiac CT and transesophageal echocardiography are also used to define the device size. Transesophageal echocardiography is used during the device implantation to ensure the best prosthesis–patient match, to assess prosthesis position and function after deployment, and to identify immediate complications (e.g., aortic insufficiency, paravalvular

leak resulting from patient–prosthesis mismatch). Echocardiography is the imaging modality of choice for long-term surveillance.

Assessment of Aortic Regurgitation Assessment of aortic regurgitation requires qualitative assessment of the aortic valve structure. Aortic regurgitation is common with congenital abnormalities of the aortic valve, the most common of which is bicuspid aortic valve. Aortic regurgitation often coexists with aortic stenosis, and it is not uncommon for patients to have both severe aortic stenosis and regurgitation. Congenital abnormalities of the aortic leaflets, such as bicuspid aortic valve, are common causes of aortic insufficiency. Dilatation of the aortic root, as occurs in patients with hypertension and other disorders in which aortic dilatation can occur, can also lead to aortic regurgitation even when the valve leaflets are intrinsically normal due to malcoaptation of the leaflets. Aortic root dilatation is common in patients with aortic regurgitation, both as a cause or coexisting lesion, and the aortic root and ascending aorta should be measured and followed in these patients (**Fig. 248-19**).

Because aortic regurgitation can result in dilatation of the left ventricle over time with ultimate reduction in ventricular function, caring for the patient with aortic regurgitation requires serial assessment of ventricular size and function. Patients whose ventricles dilate beyond an end-systolic diameter of 5.5 cm or whose LVEF declines below normal are at significantly higher risk of death or heart failure, and these measures are often used to decide the need for valve surgery. Quantitation of regurgitation itself can be performed using a number of methods. Semiquantitative visual assessment of aortic regurgitant jet width and depth by color flow Doppler remains the most used. The jet diameter as a ratio of the left ventricular outflow tract diameter proximal to the valve represents one of the most reliable indices of severity and correlates well with angiographic assessment. Similarly, the vena contracta, which represents the smallest diameter of the regurgitant flow at the level of the valve, can be used to assess the severity of aortic regurgitation. Other Doppler-based methods include assessing the pressure half-time, or rate of decline of the pressure gradient between the aorta and left ventricle, a measure of acuity of aortic regurgitation, and assessing aortic flow reversal in the descending aorta.

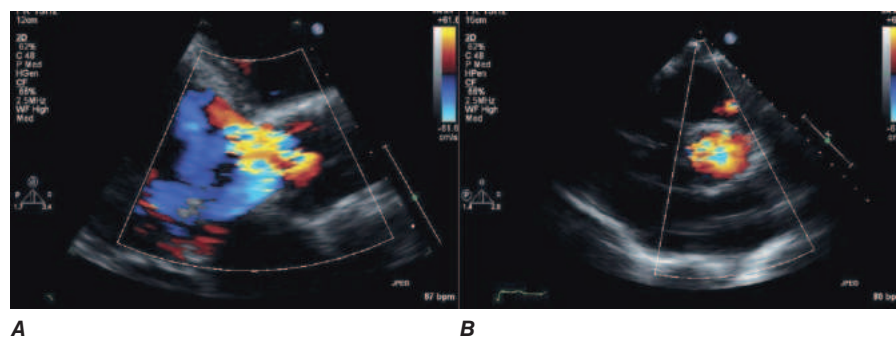


FIGURE 248-19 Aortic regurgitation visualized by color flow Doppler in the parasternal long-axis view (**A**) and the parasternal short-axis view (**B**).

The regurgitant volume can be calculated by comparing the flow across the aortic and pulmonic valves, assuming the pulmonic valve is competent. Central or perivalvular aortic regurgitation is common in patients following transcatheter aortic valve replacement and is generally assessed immediately after the procedure and on follow-up echocardiography.

CMR offers several advantages over echocardiography in the assessment of aortic regurgitation. CMR is more accurate than echocardiography for assessing small changes in cardiac size or function longitudinally in patients with aortic insufficiency. In addition, CMR can accurately quantify aortic regurgitant volume secondary to aortic insufficiency better than echocardiography. CMR can also capture aortic size in 3D that may be helpful in determining the etiology of the aortic regurgitation or in monitoring progression of the condition (Fig. 248-20 and Video 248-6). For this reason, CMR is often used for serial follow-up of patients with aortic regurgitation.

Assessment of Mitral Regurgitation The normal mitral valve consists of an anterior and posterior leaflet in a saddle shape configuration (Fig. 248-21). The leaflets are attached to the papillary muscles via chordae tendineae that insert on the ventricular side of the leaflets. Mitral regurgitation can occur due to abnormalities of the leaflets, the chordal structures, or the ventricle, or any combination of these (Fig. 248-22).

Mitral valve prolapse, in which one leaflet moves behind the plane of the other leaflet, can be due to myxomatous degeneration of the valves and leaflet redundancy, disruption of chordal structures secondary to degenerative disease, or papillary muscle rupture or dysfunction following myocardial infarction. Regurgitant jets can be visualized using color flow Doppler. The velocity of regurgitant jets is driven by the pressure gradient between the two chambers. This velocity will thus be quite high for left-sided regurgitant lesions, including mitral

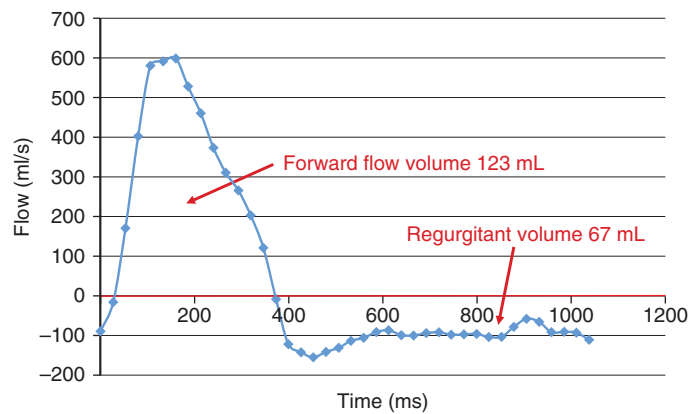


FIGURE 248-20 The resultant flow curve generated from phase contrast imaging demonstrates a forward flow of 123 mL and a regurgitant volume of 67 mL, yielding a regurgitant fraction of 54% indicating severe aortic regurgitation.

regurgitation and aortic regurgitation, resulting in turbulent jets on color flow Doppler (Fig. 248-22). Visual estimation of color flow Doppler is generally sufficient for qualitative assessment of regurgitant severity but can dramatically under- or overestimate regurgitation severity, particularly when regurgitant jets are quite eccentric. For this reason, quantitative assessment is generally recommended, especially when making clinical decisions about surgical intervention. The proximal isovelocity surface area (PISA) method is generally used for quantitative assessment of severity of mitral regurgitation. This method relies on estimation of the velocity of flow acceleration at a specific distance proximal to the valve with the assumption that the flow accelerates in concentric hemispheres.

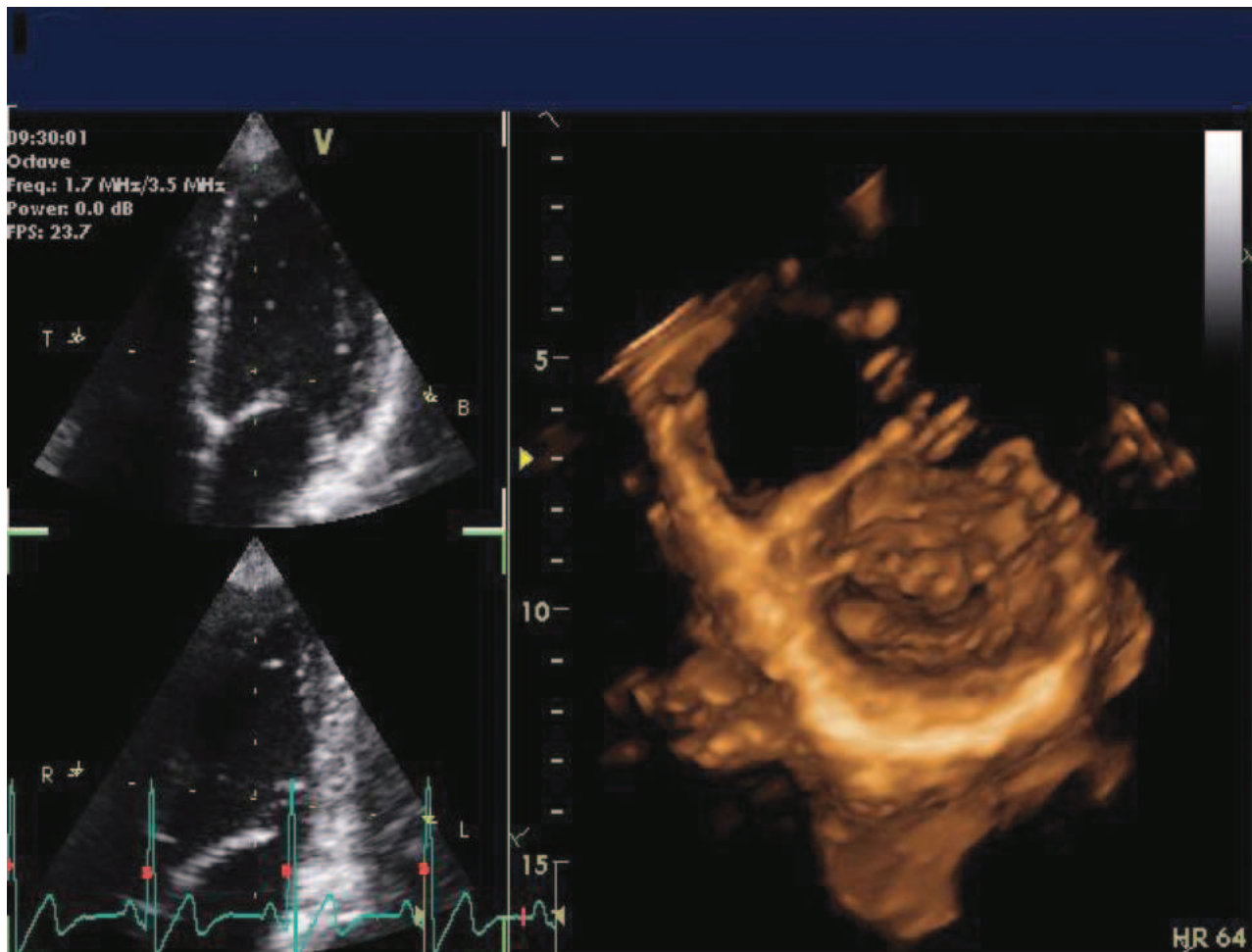


FIGURE 248-21 Normal mitral valve in two-dimensional views (left) and with three-dimensional imaging (right).

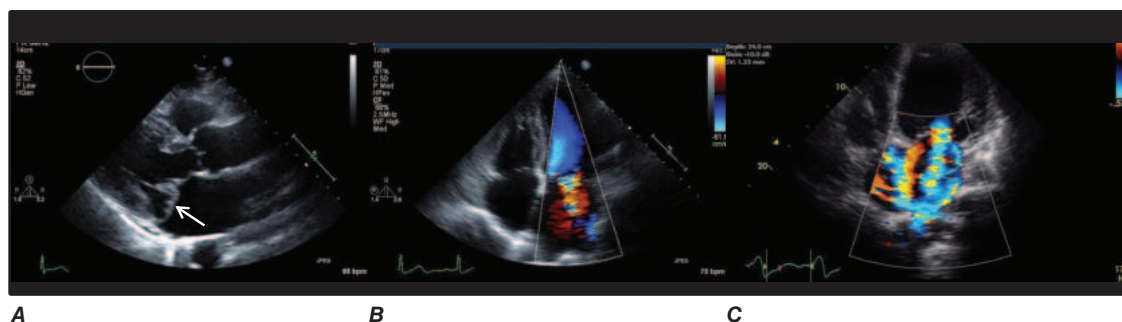


FIGURE 248-22 **A.** Mitral valve prolapse with posterior leaflet visualized prolapsing behind the plane of the anterior leaflet (arrow). **B.** Color flow Doppler showing mitral regurgitation in a patient with mitral valve prolapse. **C.** Severe functional mitral regurgitation in a patient with a dilated left ventricle.

As with aortic insufficiency, assessment of ventricular structure and function is also integral in the evaluation of mitral regurgitation. Although some patients have mitral regurgitation due to intrinsic abnormalities of the valve itself, in others, the valve can be relatively normal, but the mitral regurgitation can be secondary to dilatation and remodeling of the left ventricle. So-called functional mitral regurgitation is generally secondary to apical displacement of the papillary muscles in a dilated ventricle, resulting in the leaflets of the mitral valve being pulled toward the apex of the heart, resulting in poor coaptation during systole and resultant relatively central mitral regurgitation. This type of mitral regurgitation can generally be distinguished from intrinsic mitral valve disease, and the surgical or procedural treatment of these conditions can be different. Knowledge of the etiology of mitral regurgitation can be important for a surgeon planning mitral valve surgery. Moreover, new procedural approaches to mitral valve disease may be different depending on the etiology.

Ventricular dilatation is an important predictor of outcome in patients with mitral regurgitation of any cause. It is important to realize that in a patient with significant mitral regurgitation, a large portion of the blood being ejected from the left ventricle with every beat is regurgitant, thus artificially increasing the ejection fraction. Thus, an ejection fraction of 55% in a patient with severe mitral regurgitation may represent substantial reduction in myocardial systolic function.

CMR can be helpful in evaluating mitral regurgitation in a subset of patients when echocardiographic assessment is inadequate. CMR can directly quantify regurgitant volume of the mitral regurgitant jet or indirectly quantify regurgitant volume by measuring the difference of left ventricular stroke volume and aortic forward flow.

Assessment of Mitral Stenosis Rheumatic mitral disease remains the most common cause of mitral stenosis, although mitral stenosis can also result from severe calcification of the mitral leaflets. Rheumatic mitral stenosis has a distinct appearance characterized by tethering at the leaflet tips and relative pliability of the leaflets themselves, resulting in a hockey stick-type deformation particularly of the anterior leaflet (Fig. 248-23). Narrowing of the mitral orifice impedes flow from the left atrium to the left ventricle, resulting in

increased pressures in the left atrium, which are then transmitted backward into the pulmonary vasculature and the right side of the heart. When mitral stenosis is suspected, echocardiography can be useful for determining etiology (specifically whether it is rheumatic or not), estimating the valve areas and gradients across the valve, assessing the left atrium, and assessing right ventricular size and function. Assessment of left atrial size and right ventricular size and function is particularly useful in helping determine the severity of the mitral stenosis.

■ MYOCARDIAL INFARCTION AND HEART FAILURE

Role of Imaging after Myocardial Infarction Imaging can be useful in the immediate and long-term follow-up of patients with myocardial infarction. As discussed earlier in the chapter, LGE imaging by CMR is the best technique for imaging for presence or the extent of infarcted myocardium. In a recent multicenter study, LGE imaging identified infarct location accurately and detected acute and chronic infarcts at a sensitivity of 99 and 94%, respectively. In addition, regions of microvascular obstruction (no-reflow) can be seen as dense hypoenhanced areas within the core of a bright region of infarction (Fig. 248-24). Both the presence of LGE and microvascular obstruction are markers of increased clinical risk.

While echocardiography is often used to assess myocardial function immediately after myocardial infarction, myocardial stunning is common in the early post-myocardial infarction period, especially in patients who undergo reperfusion therapy. In these patients, either partial or complete recovery of ventricular function is common within several days, so that early estimation of ejection fraction may be misleading. In patients with uncomplicated myocardial infarction, imaging can generally be deferred for several days so that a more accurate assessment of cardiac function, including regional wall motion, can be assessed (Fig. 248-25).

Echocardiography is the best method for assessment of patients with suspected mechanical complications after myocardial infarction. These include mitral regurgitation secondary to either papillary muscle dysfunction or rupture of papillary muscle head, ventricular septal defect, or cardiac rupture. A new severe systolic murmur should raise

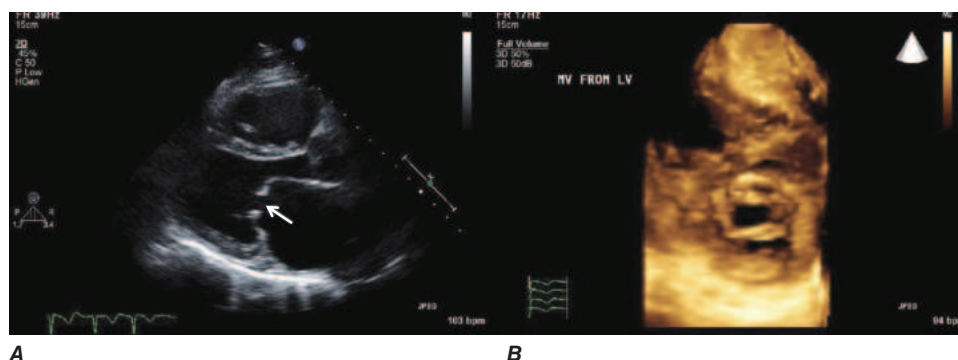


FIGURE 248-23 **A.** Rheumatic mitral stenosis showing pliable leaflets tethered at the tips (arrow). Note the characteristically enlarged left atrium. **B.** Mitral stenosis visualized from a three-dimensional echocardiogram.

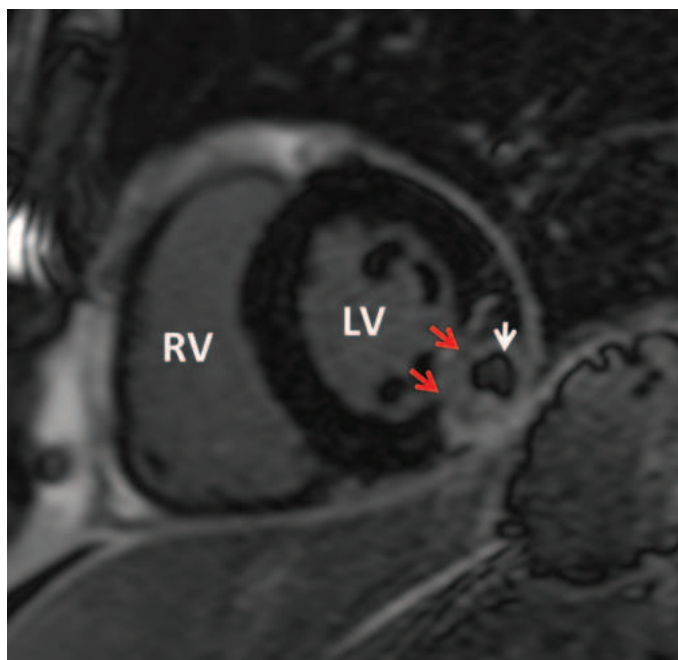


FIGURE 248-24 Example of a patient who presented with inferior ST-segment elevation myocardial infarction (MI) after several days of intermittent chest pain. Magnetic resonance imaging (MRI) confirmed an inferior MI by the location of late gadolinium enhancement (LGE; red arrows). In addition, there is a central area of microvascular obstruction (dark region surrounded by the bright LGE, white arrow). LV, left ventricle; RV, right ventricle.

suspicions for either severe mitral regurgitation or ventricular septal defect. While cardiac rupture is often catastrophic, contained ruptures, in the form of pseudoaneurysms, can occur, and early diagnosis and surgical treatment are the best way to maximize survival. The presence of thrombus within the pericardial space following myocardial infarction should immediately raise suspicion of myocardial rupture and represents a surgical emergency.

Some patients demonstrate progressive left ventricular dilation and dysfunction, known as cardiac remodeling, after myocardial infarction. Assessment of cardiac function and regional wall motion is useful in the follow-up period, generally between 1 and 6 months following infarction. The persistence of left ventricular systolic dysfunction following infarction is used to determine the type of therapy (e.g., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are typically used in patients with systolic dysfunction following myocardial infarction).

In patients with acute or subacute myocardial infarction, investigation of residual ischemia and/or viability is occasionally an important clinical question, especially among those with recurrent symptoms after

myocardial infarction (Fig. 248-26). All cardiac imaging techniques can provide information regarding myocardial viability and ischemia. The available data suggest that radionuclide imaging, especially PET, is highly sensitive, with higher negative predictive value than dobutamine echocardiography. In contrast, dobutamine echocardiography tends to be associated with higher specificity and positive predictive accuracy than the radionuclide imaging methods. The experience with CMR suggests that it offers similar predictive accuracies as those seen with dobutamine echocardiography.

Role of Imaging in New-Onset Heart Failure Echocardiography is usually a first-line test in patients presenting with new-onset heart failure. As discussed above, this test provides a direct assessment of ventricular function and can help distinguish patients with reduced from those with mildly reduced or preserved ejection fraction, particularly important because of the different therapeutic options available for patients with each of these types of heart failure. In addition, it provides additional structural information including an assessment of valves, myocardium, and pericardium.

Although coronary angiography is commonly performed in patients with reduced ejection fraction, the determination of heart failure etiology in an individual patient may be difficult even if angiographically obstructive CAD is present. Indeed, patients with heart failure and no angiographic CAD may have typical angina or regional wall motion abnormalities on noninvasive imaging, whereas patients with angiographically obstructive CAD may have no symptoms of angina or history of myocardial infarction. Thus, the appropriate classification for any given patient is not always clear, and it often requires the complementary information of coronary angiography and noninvasive imaging. As discussed above, stress radionuclide imaging and echocardiography can be helpful in delineating the extent and severity of inducible myocardial ischemia and viability. Multiparametric CMR can be quite helpful in the differential diagnosis of heart failure etiologies. Apart from quantifying left and right ventricular volumes and function, CMR can provide information about myocardial ischemia and scar. The pattern of LGE helps differentiate infarction (typically starting in the subendocardium and involving a coronary territory) from other forms of infiltrative or inflammatory cardiomyopathies (typically involving the mid- or subepicardial layers without following a coronary distribution) (Fig. 248-27). In addition, it can assess the presence of myocardial edema using T1 or T2 tissue mapping methods to inform toward chronicity of acute coronary syndromes or noncoronary inflammatory conditions (e.g., myocarditis). Other methods such as T2* mapping of myocardial iron deposition assess for the extent of iron infiltration that leads to cardiac toxicity. Infiltrative cardiomyopathy such as amyloidosis typically has a restrictive cardiomyopathy pattern characterized by biventricular increased wall thickness and bilateral atrial enlargement, as assessed by both echocardiography and CMR. CMR of patients with cardiac amyloidosis often also demonstrates a characteristic pattern of diffuse endocardial infiltration of the left ventricle and the atria (Fig. 248-27). On strain echocardiography, patients with cardiac amyloidosis show reduction in systolic function which typically spares the apical left ventricular segments. Bone scintigraphy complements the use of echocardiography and CMR in cardiac amyloidosis by allowing accurate noninvasive distinction of transthyretin (ATTR) from light chain (AL) cardiac amyloidosis. ATTR typically shows intense ^{99m}Tc tracer uptake compared to patients with AL amyloidosis (Fig. 248-28). Hypertrophic cardiomyopathy has variable degree of increased ventricular thickness and often is seen to have outflow obstruction and intense LGE in regions with marked hypertrophy (Fig. 248-29). CMR also can quantify myocardial iron content in patients at risk of iron-overload cardiomyopathy (Video 248-7).

PET metabolic imaging has a complementary role in the evaluation of inflammatory cardiomyopathies, especially sarcoidosis where the presence of focal and/or diffuse glucose uptake can help identify areas of active inflammation. In addition, for patients undergoing immunosuppressive therapy, PET is frequently used to monitor therapeutic response (Fig. 248-30). In patients with ischemic cardiomyopathy,

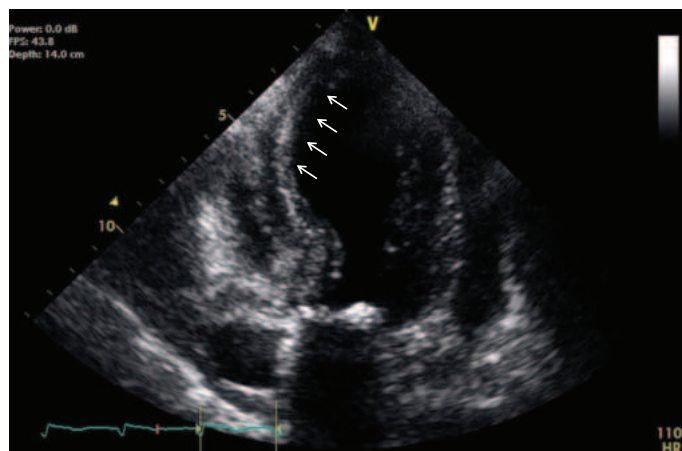


FIGURE 248-25 Acute left anterior descending artery distribution myocardial infarction at end systole showing akinetic region (arrows).

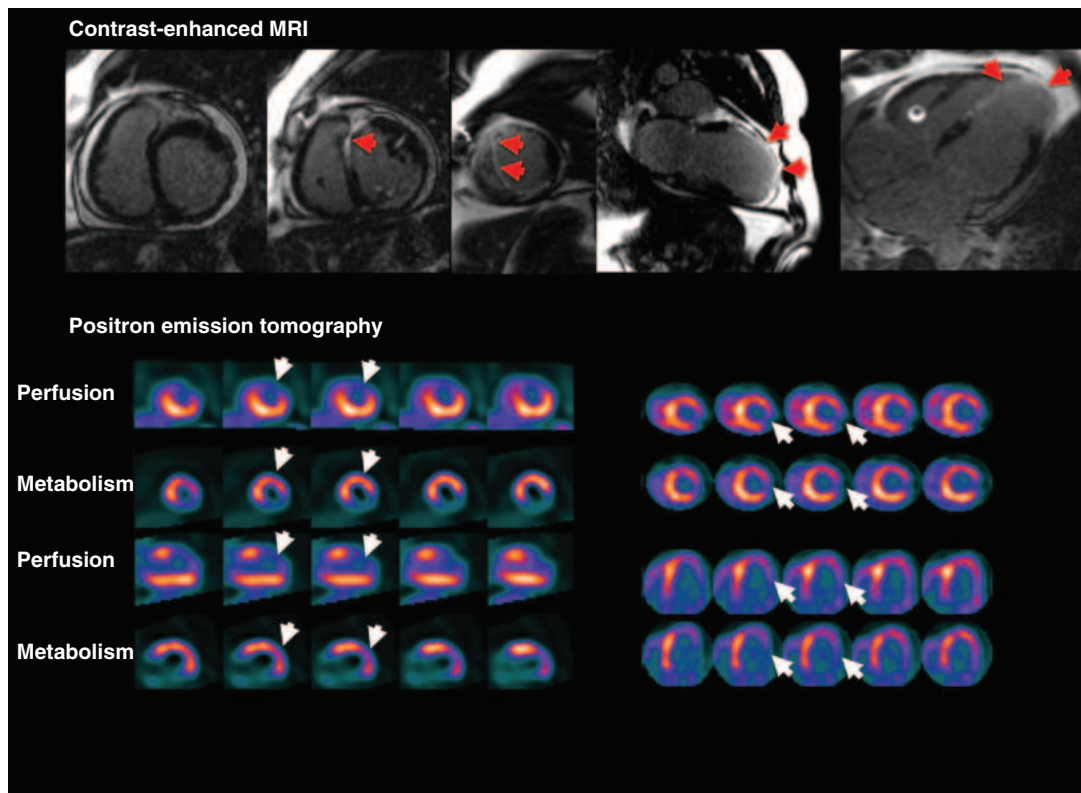


FIGURE 248-26 Examples of myocardial viability patterns obtained with cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET) in three different patients with coronary artery disease. The *top panel* demonstrates extensive late gadolinium enhancement (*bright white areas*) involving the anterior, anteroseptal, and apical left ventricular walls (*arrows*), consistent with myocardial scar and nonviable myocardium. The *lower left panel* demonstrates rubidium-82 myocardial perfusion and ^{18}F -fluorodeoxyglucose (FDG) images showing a large and severe perfusion defect in the anterior, anterolateral, and apical walls, indicating preserved glucose metabolism (so-called *perfusion-metabolic mismatch*) consistent with viable myocardium. The *right lower panel* shows similar PET images demonstrating concordant reduction in perfusion and metabolism (so-called *perfusion-metabolic match*) in the lateral wall, consistent with nonviable myocardium.

radionuclide imaging in general and PET in particular are frequently used to quantify the presence and extent of myocardial ischemia and viability to assist with clinical decision-making related to myocardial revascularization (Fig. 248-25).

■ ASSESSING CARDIAC FUNCTION IN PATIENTS UNDERGOING CANCER TREATMENT

Therapies used to treat cancer can adversely affect the cardiovascular system. As the efficacy of cancer treatment and survival improve, many patients are presenting with late adverse consequences from chemotherapy and/or radiation therapy on cardiovascular function. Thus, the morbidity and mortality from late cardiovascular complications threaten to offset the early gains in cancer survival, especially among children and young adults. Early recognition and treatment of cardiomyocyte injury are critical for successful application of preventative therapies, but difficult because the adverse effects on cardiac function are a relatively late manifestation after exposure to anticancer therapy.

The accepted standard for clinical diagnosis of cardiotoxicity is defined as a $>5\%$ reduction in LVEF to $<55\%$ with symptoms of heart failure, or a $>10\%$ drop in LVEF to $<55\%$ in patients who are asymptomatic. Thus, noninvasive imaging plays a major role in diagnosing and monitoring for cardiac toxicity in patients undergoing cancer treatment. Radionuclide angiography has been the technique of choice for quite some time. However, echocardiography now plays a major role in this application.

Recently, more novel imaging approaches have been advocated, including deformation imaging with echocardiography and fibrosis imaging with CMR. These techniques have shown promising results in experimental animal models and in humans. In addition, there are also proof-of-concept studies in animal models using molecular imaging approaches targeting the mechanisms of cardiac toxicity (e.g., apoptosis and oxidant stress), which can presumably provide the earliest signs of the off-target effects of these therapies. However, these techniques are currently considered experimental.

■ PERICARDIAL DISEASE

The fibroelastic pericardial sac surrounding the heart consists of a visceral, or epicardial, layer and a parietal layer, with a generally small amount of pericardial fluid in between layers. The pericardium is generally quite pliable and moves easily with the heart during contraction and relaxation. Abnormalities of the pericardium can affect cardiac function primarily by impairing the heart's ability to fill. Inflammation of the pericardium can lead to an accumulation of fluid between the two layers, or *pericardial effusion*, which can be visualized by echocardiography, CMR, or CT. Other reasons for accumulation of pericardial fluid include infection, malignancy, and bleeding into the pericardium. The latter can be the result of catastrophic processes such as trauma, cardiac rupture, perforation in the setting of a cardiac procedure, cardiac surgery, or dissection of the aorta with extension in the pericardium.

Echocardiography remains the initial test of choice for assessing pericardial disease, especially effusions (Fig. 248-31). Moreover, echocardiography can be useful in evaluating for pericardial constrictive physiology, in which a thick noncompliant pericardium impairs cardiac filling. The location, size, and physiologic consequences of accumulated pericardial effusion can generally easily be determined by echocardiography. Pericardial tamponade occurs when enough pericardial fluid accumulates so that the intrapericardial pressure exceeds filling pressures of the heart, generally the right ventricle. The balance between intrapericardial pressure and ventricular pressure is more important than the extent of fluid accumulation. Conditions in which pericardial effusions accumulate over a long period of time, as can be the case in the setting of malignant effusions, can lead to large pericardial fluid accumulations without the classic hemodynamic findings associated with pericardial tamponade. In contrast, rapid accumulations of pericardial fluid, such as those that occur due to cardiac rupture or perforation, can lead to tamponade physiology without very large effusions. In patients with suspected pericardial effusion or tamponade, echocardiography can usually be performed rapidly, at the

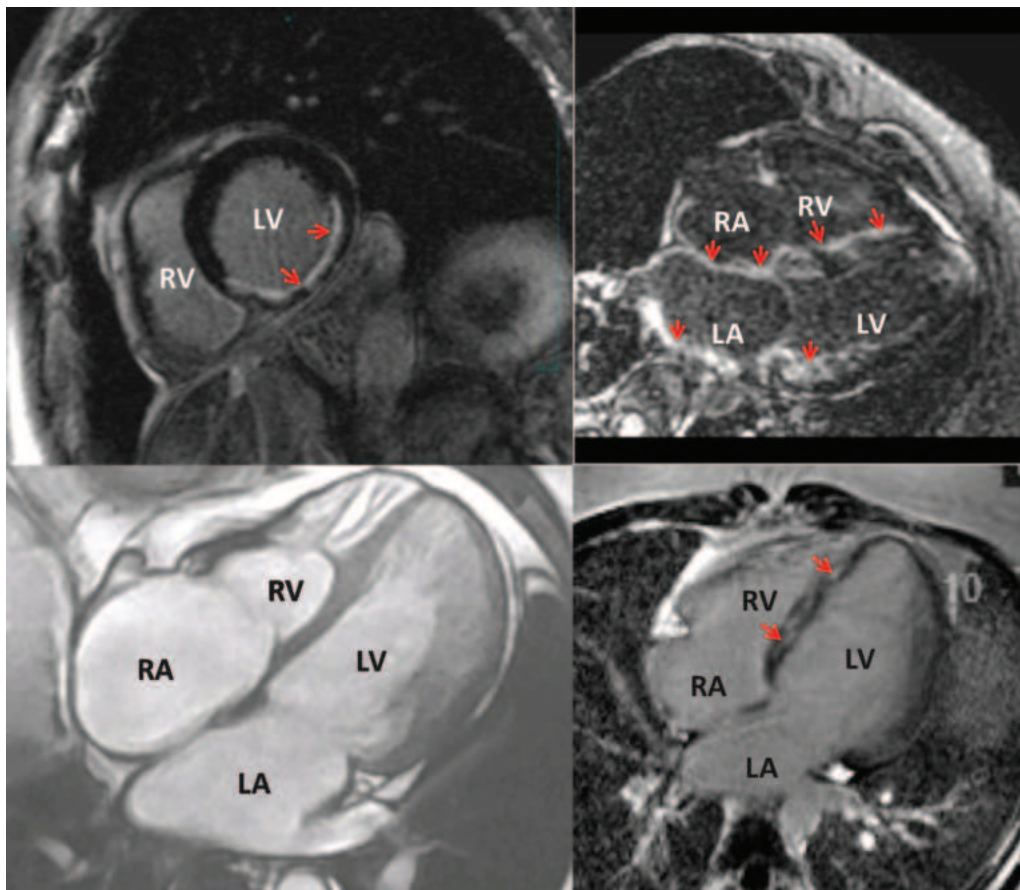


FIGURE 248-27 Differentiation of various cardiomyopathies by cardiac magnetic resonance (CMR). The *left upper panel* shows the short-axis late gadolinium enhancement (LGE) imaging of a patient who suffered an acute myocardial infarction. Note LGE of the endocardial myocardium in the inferior wall extending from the septum to the lateral wall associated with myocardial thinning (arrows). The *right upper panel* shows the long-axis LGE imaging of a patient who has cardiac amyloidosis. Note the diffuse LGE throughout left ventricular myocardium, the left atrium, and the interatrial septum (arrows). In addition, the blood pool is characteristically dark in signal, indicating sequestration of gadolinium contrast out of the blood pool after injection due to a high burden of amyloidosis in other organs. The *left lower panel* shows a cine diastolic long-axis image of a patient with a nonischemic dilated cardiomyopathy. Note that there is extensive sponge-like noncompacted myocardium of the LV as well as dilatation of all four cardiac chambers. This patient has a nonischemic dilated cardiomyopathy secondary to LV noncompaction. The *right lower panel* shows a 22-year-old female patient with a recent episode of acute chest pain and troponin elevation. Note the multiple mid-wall foci of LGE, which suggests acute myocarditis (arrows). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

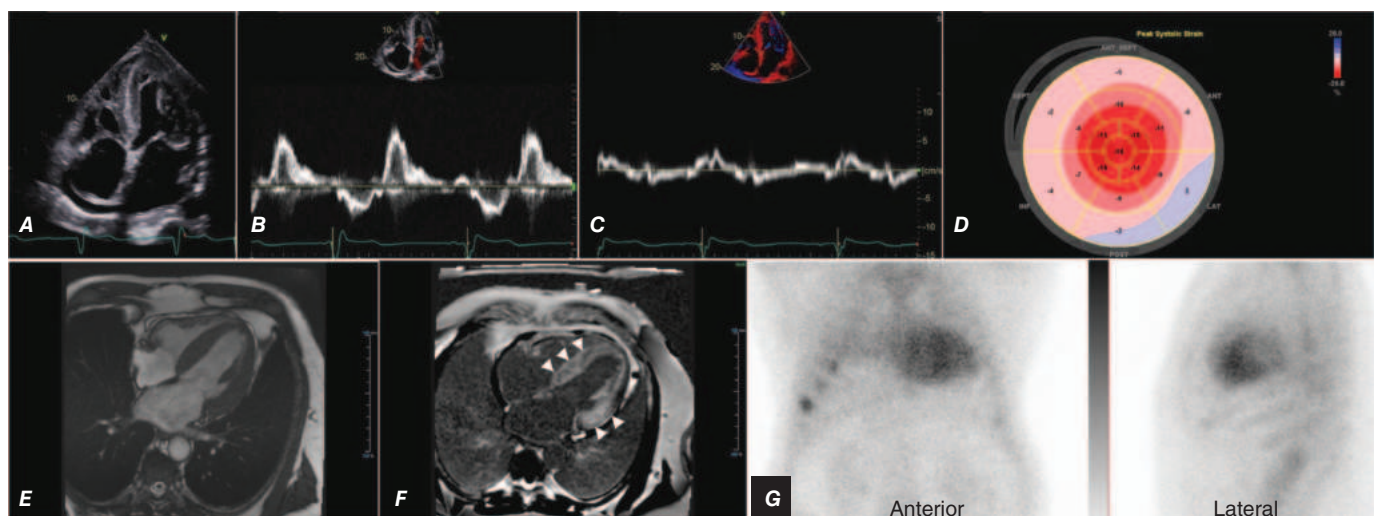


FIGURE 248-28 Multimodality cardiac imaging in a 71-year-old man with history of atrial fibrillation, heart failure with preserved ejection fraction, numbness in his fingers, a history of bilateral carpal tunnel surgery, and remote history of back surgery with L3 and S1 fusion. **A.** Two-dimensional echocardiogram demonstrating moderate increase in left ventricular thickness with a visually estimated left ventricular ejection fraction of 45–50% and small pericardial effusion. **B, C.** Mitral inflow and tissue Doppler demonstrating abnormal diastolic function (E/e' was >20 , consistent with elevated left ventricular filling pressure). **D.** Bull's-eye strain map demonstrating abnormal global longitudinal strain at the basal segments (pink and blue colors) with characteristic apical sparing (red color). **E.** Cardiac magnetic resonance imaging (MRI) study showing normal left ventricular (LV) cavity size and mildly increased LV mass and mildly enlarged right and left atria. **F.** The MRI shows a large amount of diffuse late gadolinium enhancement of all myocardial LV segments but more prominent in a circumferential subendocardial pattern (arrowheads). **G.** The ^{99m}Tc -pyrophosphate images demonstrate increased myocardial uptake of the radiotracer (uptake in the heart is greater than ribs, grade 3). (Images courtesy of Dr. Sarah Cuddy, Brigham and Women's Hospital.)

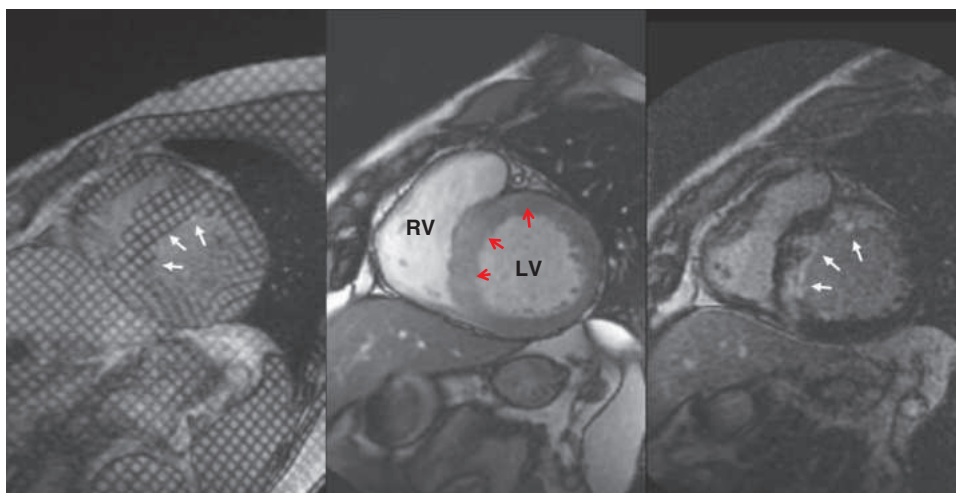


FIGURE 248-29 This figure demonstrates three pulse sequence techniques by cardiac magnetic resonance that are often used to assess patients with hypertrophic cardiomyopathy, all displayed in the mid short-axis scan plane. The *center panel* demonstrates that the left ventricle (LV) was markedly thickened in its wall thickness especially in the LV septum (*red arrows*). This finding was matched by marked regions of late gadolinium enhancement (LGE), which was consistent with fibrosis in these segments (*right panel, white arrows*). The *left panel* was cine myocardial tagging in the same slice plane. Myocardial tagging is used to assess the normal intramyocardial strain by assessing distortion of the myocardial grids during systole. In this case, despite normal-appearing systolic radial wall thickening, the myocardial strain as assessed by the distortion of grids was markedly reduced (*left panel, white arrows*). This finding is consistent with substantial myofibril disarray in the anterior and antero-septal segments in this patient. RV, right ventricle.

bedside, and even by operators with limited skill. The distance from the parietal to the visceral pericardial layer can be measured, and when this exceeds ~1 cm, an effusion is considered significant. Echocardiographic features suggestive of tamponade include diastolic collapse of the right ventricular free wall, suggestive of pericardial pressures that exceed right ventricular filling pressures, and Doppler evidence of respiratory flow variation, which is the Doppler equivalent of pulsus paradoxus. Despite the benefits of echocardiography in suspected pericardial tamponade, the diagnosis of tamponade remains a clinical diagnosis, and other important features, such as patient's blood pressure in the presence of pulsus paradoxus, need to be considered when weighing therapeutic options.

Chronic inflammation of the pericardium leads to thickening and calcification of the parietal pericardium, resulting in pericardial constriction in which diastolic filling can be severely impaired. In these cases, filling of the ventricles comes to an abrupt halt when the volume of ventricular filling is impaired by the constricting pericardium. Assessment of pericardial thickness in these patients is important, but it is just as important to note that approximately one in five patients with severe pericardial constriction have no significant pericardial thickening by imaging or at surgery. Thus, a lack of thickened pericardium does not rule out pericardial constriction, and patients' signs and symptomatology and physiologic evidence of constriction should be assessed independently. Pericardial constriction typically demonstrates

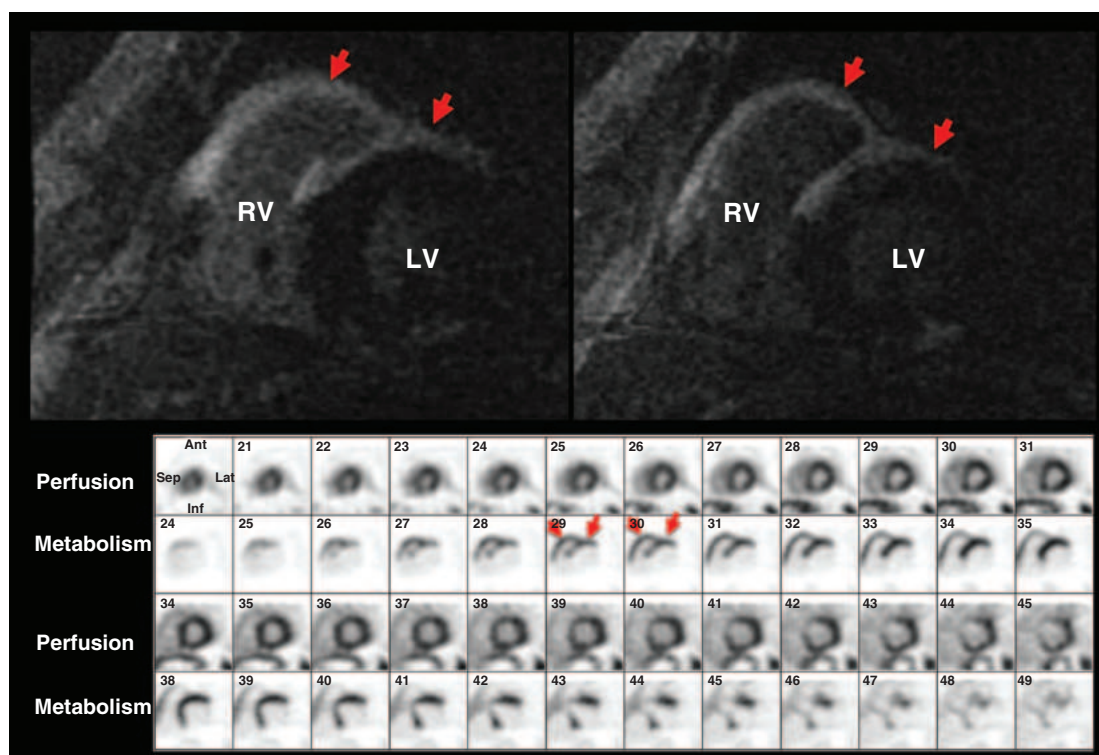


FIGURE 248-30 Representative cardiac magnetic resonance (CMR; *top panel*) and positron emission tomography (PET; *lower panel*) images from a 45-year-old male presenting with complete heart block. The CMR images demonstrate extensive late gadolinium enhancement in the subepicardial left ventricular (LV) anterior and antero-septal walls and also in the right ventricular (RV) free wall (*arrows*). The PET images demonstrate extensive fluorodeoxyglucose uptake in the same areas, most consistent with active inflammation due to sarcoidosis.

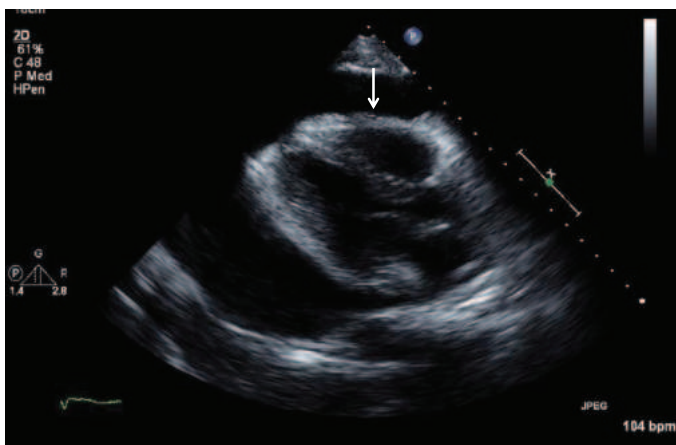


FIGURE 248-31 Pericardial effusion with tamponade physiology. The right ventricle (arrow) is small and collapsing in end diastole due to increased pericardial pressure.

marked respiratory changes in diastolic flow on Doppler echocardiography, in contrast to restrictive cardiomyopathy, but substantial overlap exists. CT and CMR offer tomographic, whole-heart assessment of pericardial thickening and other anatomy abnormalities in pericardial constriction enlarged atria, vena cava, and pleural and pericardial effusions (Figs. 248-32 and 248-33, and Videos 248-8 and 248-9). CMR offers the additional information of pericardial fibrosis and inflammation by LGE imaging and evidence of constrictive physiology (e.g., regional relaxation concordance due to myocardial adhesions, abnormal septal bounce with Valsalva maneuver) (Fig. 248-33).

■ CARDIAC THROMBUS AND MASS

Echocardiography is usually the modality that first detects a cardiac mass with differential diagnoses including thrombus, tumor, or vegetation. Given their unrestricted tomographic views and multiplanar 3D imaging, CMR and CT can complement echocardiography by further characterizing the physical features of the cardiac mass. Compared to CT, CMR has the advantage of higher tissue contrast differentiation, more robust cine imaging, and the use of multifaceted techniques within the same imaging session to determine the physiologic characteristics of the mass. Gadolinium contrast enhancement patterns of

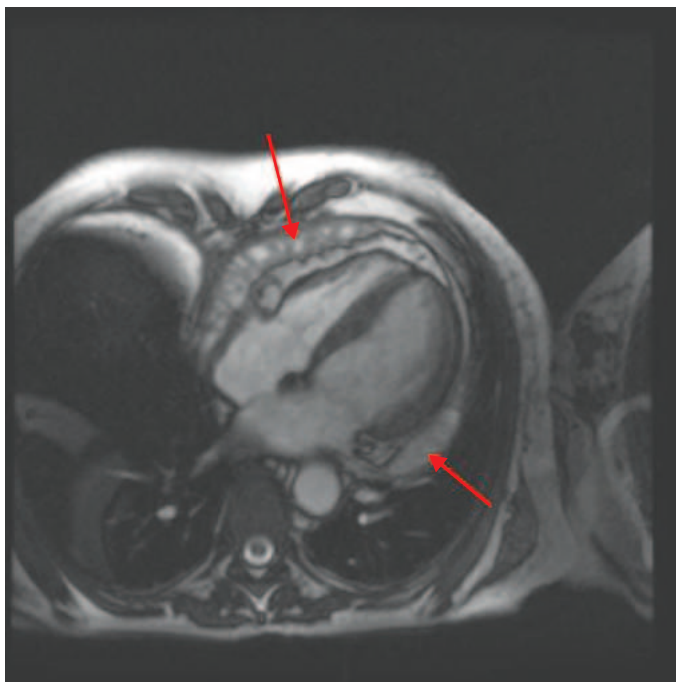


FIGURE 248-32 A female patient developed pericardial constriction and right heart failure, secondary to radiation therapy for breast cancer. Note the multiple pericardial adhesions (red arrows).

increased capillary perfusion can detect vascularity within a mass that differentiates a tumor from a thrombus. Structures that are known to mimic a cardiac mass include (1) anatomic variants, such as the Eustachian valve, Chiari network, crista sagittalis or terminalis, and the right ventricular moderator band, and (2) “pseudotumors,” such as interatrial septal aneurysm, coronary or aortic aneurysm, lipomatous hypertrophy of interatrial septum, hiatal hernia, or a catheter/pacemaker lead. Coexisting abnormalities that raise the likelihood of a cardiac thrombus (Fig. 248-34) include regional wall motion abnormality from an infarction or ventricular aneurysm, atrial fibrillation leading to slow flow in the left atrial appendage, or presence of venous catheters or recent endovascular injury. CMR has the advantage of being able to assess regional wall motion and infarction or ventricular aneurysm in matching scan planes, adjacent to the cardiac thrombus, using cine and LGE imaging, respectively. For ventricular thrombus, gadolinium-enhanced LGE imaging can detect thrombus at a higher sensitivity than echocardiography by depicting high-contrast difference between the dark thrombus and its adjacent structures and by imaging in three dimensions. In addition, mural thrombus does not enhance on first-pass perfusion and often has a characteristic “etched” appearance (black border surrounding a bright center) on LGE imaging, thus providing higher diagnostic specificity than anatomic information alone (Fig. 248-35). Comparing the signal intensities of a mass before and after contrast injection may confirm the lack of tissue vascularity (i.e., thrombus) by the lack of signal enhancement after contrast administration. Like intracardiac thrombus, regions of microvascular obstruction also appear dark, but microvascular obstruction is confined within the myocardium and surrounded by infarction and thus can be differentiated from intracardiac thrombus. Cardiac CT imaging is ideally suited for small thrombus in the left atrial appendage especially in cases where transesophageal echocardiography is suboptimal or not feasible.

Metastatic cardiac malignancy is about 20-fold more common than primary cardiac tumors. However, with the exception of involvement of the pericardium, even metastatic tumors of the heart are rare. Metastasis to the heart can be the result of direct invasion (e.g., lung and breast), lymphatic spread (e.g., lymphomas and melanomas), or hematogenous spread (e.g., renal cell carcinoma). Primary benign cardiac tumors are seen mostly in children and young adults and include atrial myxoma, rhabdomyoma, fibroma, and endocardial fibroelastoma (Fig. 248-36). Atrial myxomas are often seen as a round or multilobar mass in the left atrium (75%), right atrium (20%), or ventricles or mixed chambers (5%). They typically have inhomogeneous brightness in the center on cine steady-state free precession imaging due to their gelatinous contents and may have a pedunculated attachment to the fossa ovalis. Primary malignant cardiac tumors are rare and may include angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma.

■ ROLE OF IMAGING IN INFECTIOUS AND INFLAMMATORY DISEASE

Patients with suspected endocarditis often undergo echocardiography for the purpose of identifying vegetations or intramyocardial abscesses. Vegetations are generally highly mobile structures that most typically are attached to valves or present in areas of the heart with turbulent flow. The absence of a vegetation on echocardiography does not rule out endocarditis, because small vegetations below the resolution of the imaging techniques can be present. Echocardiography remains the best technique for assessment of vegetations because its high temporal resolution allows visualization of the typical oscillating motion, although large vegetations can be visualized with other techniques (Fig. 248-37). The size and location of a vegetation do not necessarily provide any specific information about the type of infection. Abscesses, particularly around the aortic and mitral annuli, are particularly concerning in patients with endocarditis and should be suspected in patients with prolongation of cardiac intervals in the setting of endocarditis. Visualization of both vegetations and possible abscesses is best done with transesophageal echocardiography, particularly in patients with prosthetic valves. Indeed, transesophageal echocardiography is the first test of choice in a patient with a mechanical mitral or aortic valve and

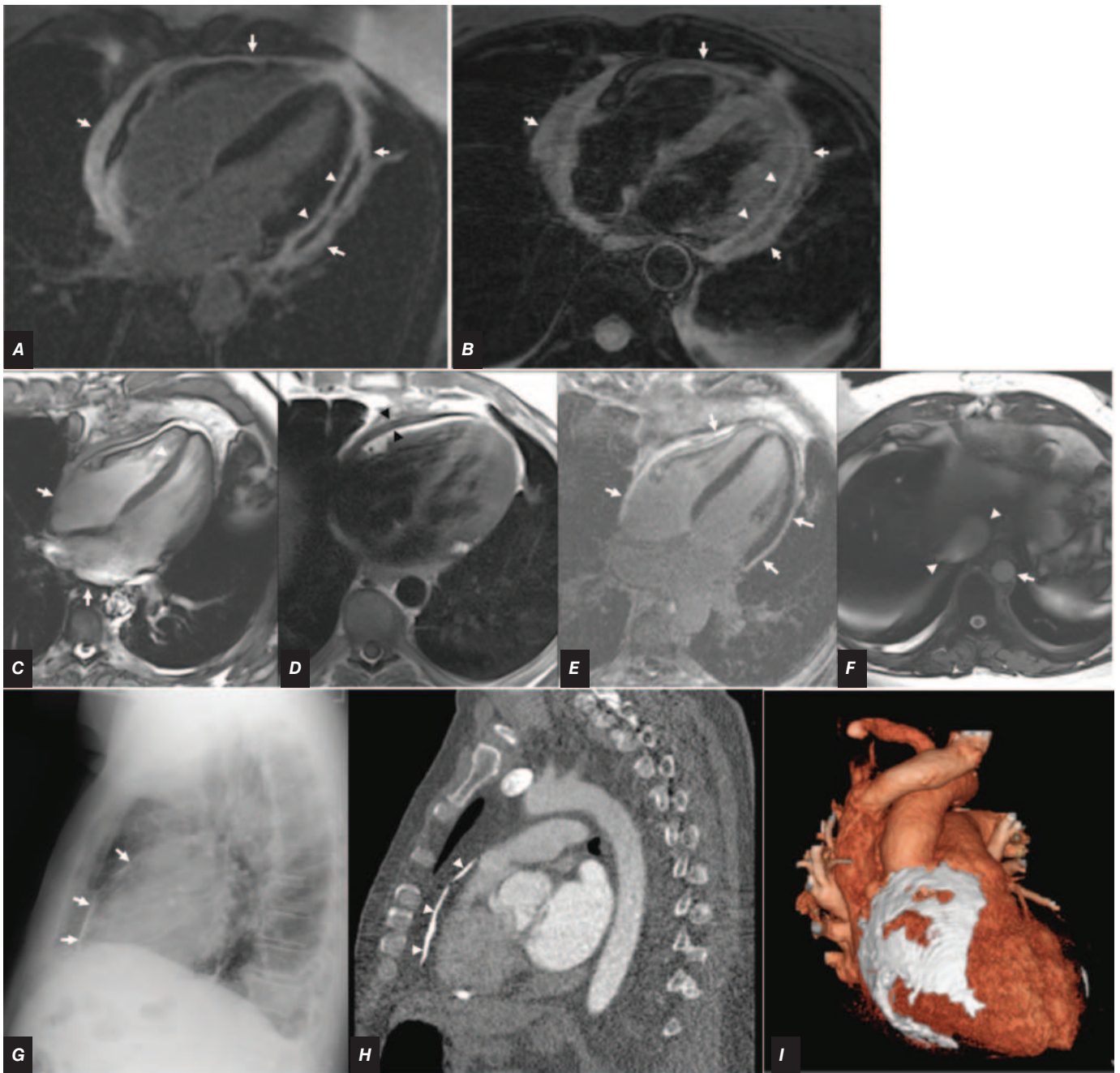


FIGURE 248-33 Representative cardiac magnetic resonance (CMR) and computed tomography (CT) features of pericardial disease. **A.** Four-chamber late gadolinium-enhanced image showing severe diffuse enhancement of both the visceral (arrowheads) and parietal (arrows) layers of the pericardium. The black signal between the two layers represents effusion. **B.** Axial T2-weighted image showing severe thickening and increased signal of both the visceral (arrowheads) and parietal (arrows) layers of the pericardium. **C.** Four-chamber steady-state free precession (bright-blood) image in early diastole showing the apical interventricular septum bowed to the left (white arrowhead) due to the increased right-sided ventricular volume at the expense of the left ventricular volume. Dilated atria (white arrows) are also a feature of constriction. **D.** Axial T1-weighted double inversion recovery (black-blood) image showing increased thickness of the pericardium >4 mm (black arrowhead). **E.** Four-chamber late gadolinium-enhanced image showing diffuse enhancement of the thickened pericardium (white arrows). **F.** Axial steady-state free precession (bright-blood) image showing dilated inferior vena cava (IVC; white arrowheads) that is greater than twice the size of the normal aorta (white arrow). Under normal conditions, the IVC should be similar in size to the aorta. **G.** Lateral chest radiograph showing calcification of the pericardium anteriorly (arrows). **H.** Corresponding sagittal view from CT angiography (CTA) showing the calcified pericardium (arrowheads). **I.** Three-dimensional rendered segmented image from the CTA showing the extent of the pericardial calcification. (Images courtesy of Dr. Michael Steigner, Brigham and Women's Hospital.)

suspected endocarditis (Fig. 248-37). Vegetations should be measured because their size has prognostic importance and can be used to decide whether a patient should be taken to surgery.

PET metabolic imaging is emerging as a potentially useful imaging technique to identify the source of infection in patients with prosthetic valves, vascular grafts, and implantable pacemakers/defibrillators, especially in patients in whom echocardiography and/or blood cultures are negative. There is an emerging literature documenting the potential value of macrophage-targeted metabolic imaging with ^{18}F -FDG and PET (Fig. 248-38). Likewise, FDG-PET is also useful to identify

vascular inflammation and monitor the response to immunosuppressive therapy (Fig. 248-39).

■ EVALUATION OF COMMON CONGENITAL ABNORMALITIES IN THE ADULT

While a discussion of complex congenital heart disease is beyond the scope of this chapter, several common congenital abnormalities are present in adults, and cardiac imaging is essential to diagnosing and managing these conditions. Abnormalities of the interatrial septum probably represent the most common adult congenital cardiac

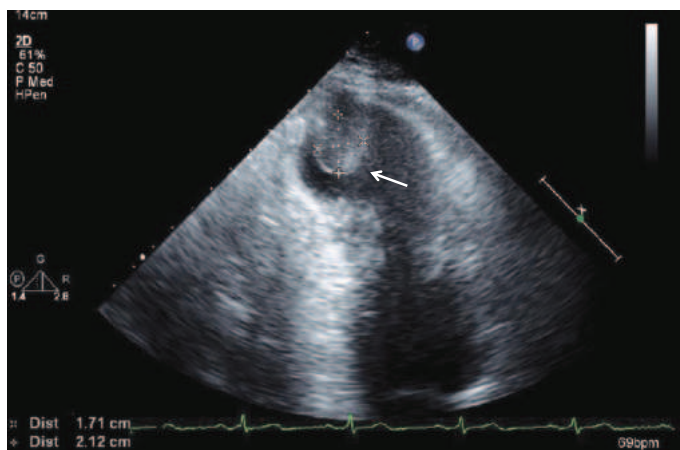


FIGURE 248-34 Cardiac thrombus (arrow) in an apical aneurysmal region following acute myocardial infarction.

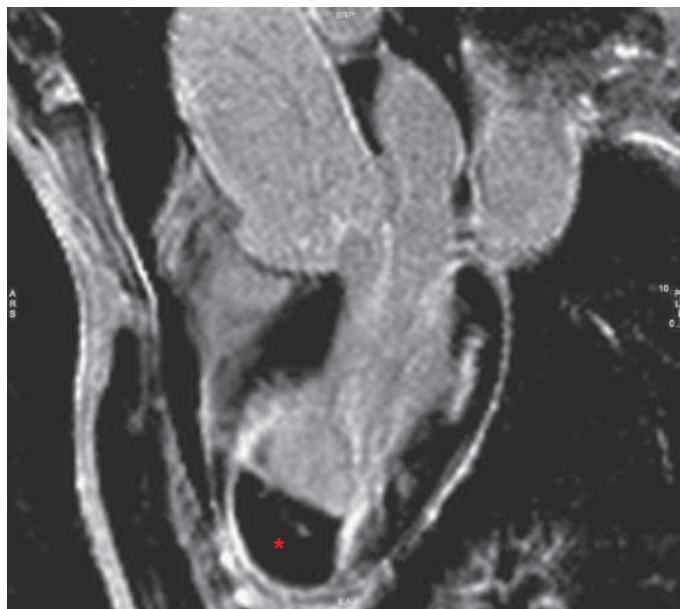


FIGURE 248-35 Late gadolinium enhancement image of a massive anterior infarction complicated by a dyskinetic left ventricular aneurysm and intracavitary thrombus (red asterisk).

abnormalities. Patent foramen ovale (PFO) can be identified in almost 25% of patients. In patients with PFO, a one-way flap in the region of the fossa ovalis is normally kept close by the left atrial pressure, which is generally higher than right atrial pressure for much of the cardiac cycle. However, right-to-left flow through a PFO can occur any time the right atrial pressure exceeds the left atrial pressure, including with maneuvers or conditions in which intrathoracic pressure is increased. The presence of a PFO can increase the likelihood of the paradoxical embolus, and thus the presence of a PFO should be determined in patients with stroke or systemic embolus of unknown etiology. Because the one-way flap of the PFO will be closed during much of the cardiac cycle, color flow Doppler will usually not reveal a PFO. Instead, agitated saline (bubble study) is the best way to assess for PFO or atrial septal defect. Saline is agitated and injected peripherally and then enters the right atrium. If no shunt is present, only the right side of the heart will be pacified because the air bubbles will be too small to traverse the lungs. Because PFO is a one-way flap, maneuvers should be used to temporarily increase right atrial pressure. Either a Valsalva maneuver or sniff maneuver can be effective.

Atrial septal defects occur most commonly in the region of the fossa ovalis, referred to as secundum-type defects (Fig. 248-40). Additional atrial septal defects include defects of the sinus venosus and atrium primum. Color flow Doppler echocardiography is usually sufficient for diagnosis of a secundum-type atrial septal defect, but agitated saline is generally needed for the diagnosis of other types of atrial septal defects.

Ventricular septal defects can generally be visualized by color flow Doppler as turbulent high-velocity jets from the left to the right ventricle. In cases where the jet origin is unclear, continuous wave Doppler can estimate the velocities. These would be expected to be extremely high to reflect the pressure gradient between the left and right ventricles. Defects can occur in both the muscular and membranous portions of the ventricular septum.

In patients with either atrial or ventricular septal defects, estimation of the severity of the left-to-right shunt is essential and can be an important determinant in management decisions. Shunts are generally assessed by echocardiography by assessing the relationship between pulmonary flow and aortic flow, the Qp/Qs ratio. Shunts and cardiac anatomy of most congenital heart diseases can also be accurately evaluated by CMR (Fig. 248-41).

ARTIFICIAL INTELLIGENCE IN CARDIAC IMAGING

Artificial intelligence (AI) is poised to revolutionize cardiac imaging over the next decade. AI methods have been applied to image acquisition, especially in echocardiography where a probe needs to

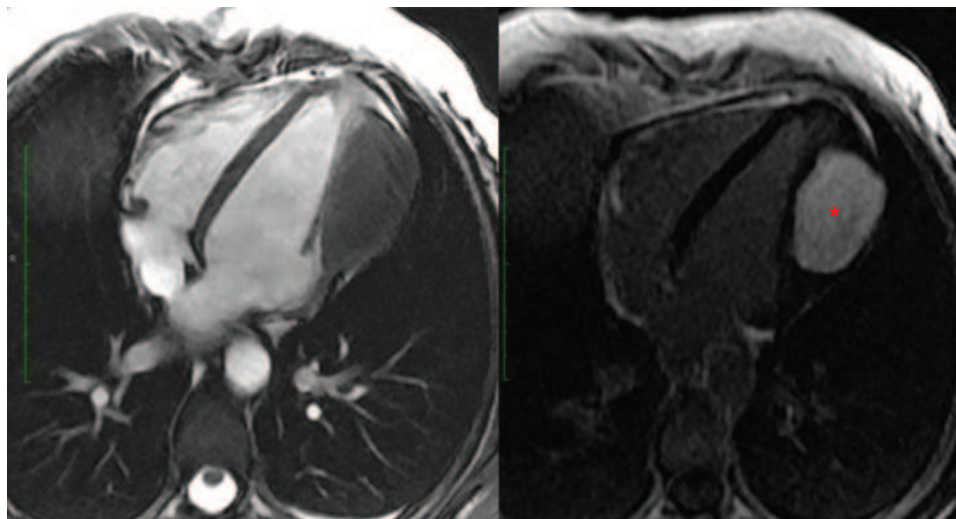


FIGURE 248-36 A case of a cardiac fibroma. A patient presented with shortness of breath and was found to have a large myocardial mass on echocardiography. Cine cardiac magnetic resonance imaging confirmed the large myocardial mass involving the anterolateral wall. Shortly after gadolinium contrast was injected, the myocardial mass demonstrated intense accumulation of contrast on late gadolinium enhancement imaging (right panel, asterisk). This is a case of cardiac fibroma. The patient also has gingival hyperplasia and bifid thoracic ribs, a part of the rare Gorlin's syndrome.



FIGURE 248-37 Vegetation on native mitral valve (*left panel, arrow*). Left atrium (LA) and left ventricle (LV) are indicated. *Middle panel* shows a vegetation on a mechanical prosthesis (St. Jude) indicated by an *arrow*; *right panel* shows vegetation on prosthesis after excision.

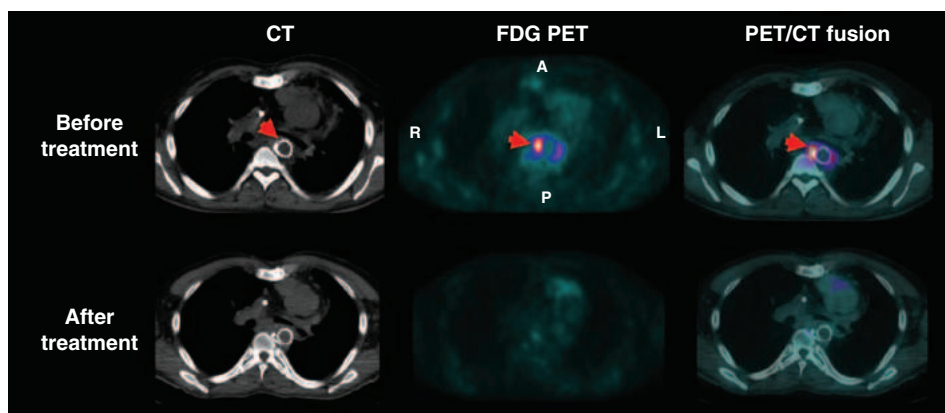


FIGURE 248-38 Representative cross-sectional computed tomography (CT; *left*), fluorodeoxyglucose (FDG) positron emission tomography (PET; *middle*), and fused CT and PET (*right*) images before and after antibiotic treatment in a patient with fever and suspected infection of the stent placed in the descending portion of the aortic arch (*arrow*) for treatment of aortic coarctation. The FDG images before treatment demonstrate intense glucose uptake within the stent, consistent with inflammation/infection. The *lower panel* demonstrates significant attenuation of the FDG signal after treatment. (Images used with permission from Dr. Sharmila Dorbala, Brigham and Women's Hospital.)

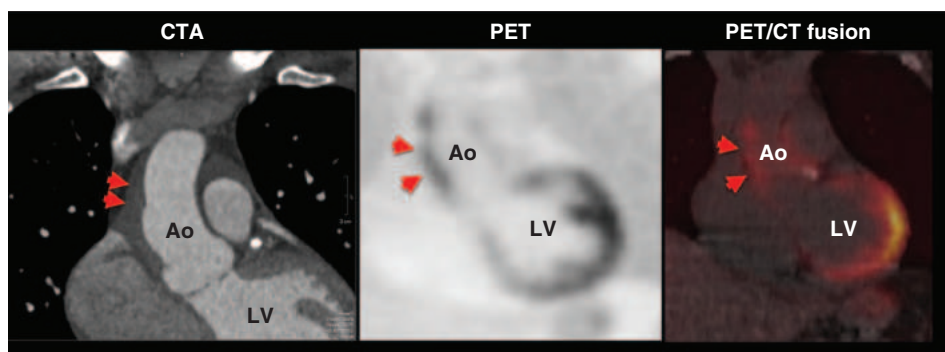


FIGURE 248-39 Representative coronal computed tomography (CT) angiographic (CTA; *left panel*), fluorodeoxyglucose (FDG) positron emission tomography (PET; *middle panel*), and fused CT and PET (*right panel*) images in a patient with suspected aortitis. The CTA images demonstrate thickening of the ascending aorta (Ao), which correlates with intense, focal FDG uptake consistent with active inflammation. LV, left ventricle.

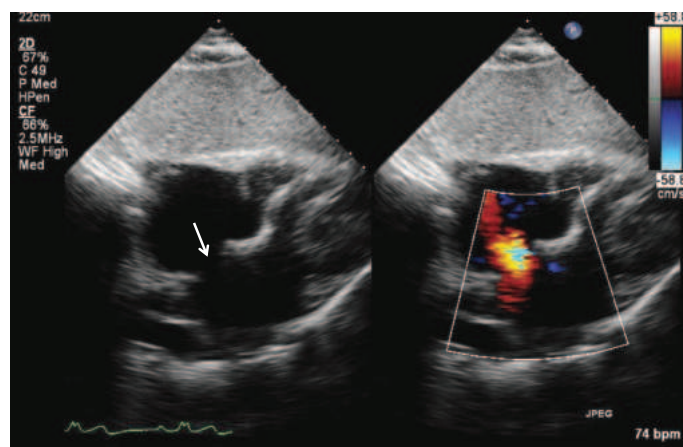


FIGURE 248-40 Large secundum-type atrial septal defect (*arrow*) noted in the subcostal view with color flow Doppler showing flow through the defect (*right*).

be manually applied to a patient's chest and the images acquired. AI software can direct a user to obtain optimal images. Likewise, cardiac MRI is a multicomponent examination that consists of numerous pulse sequences, and it is limited by the availability of an experienced scanning operator, the need for manual contouring and analysis, and a relatively long scan time of 45–60 min. FDA-approved commercial AI solutions are now available to guide the cardiac MRI scanning procedure, greatly reducing the complexities of image acquisition and reconstruction, and improving patient throughput and image quality.

AI is also being embedded in postprocessing and routine quantification. This includes image segmentation and routine measurements of cardiac dimension/volumes and function with echocardiography and CMR, quantification of CAC on nongated CT images (e.g., PET/CT and SPECT/CT), and plaque burden on coronary CTA. There is also growing evidence that AI may be able to refine risk prediction by integrating imaging markers of risk.

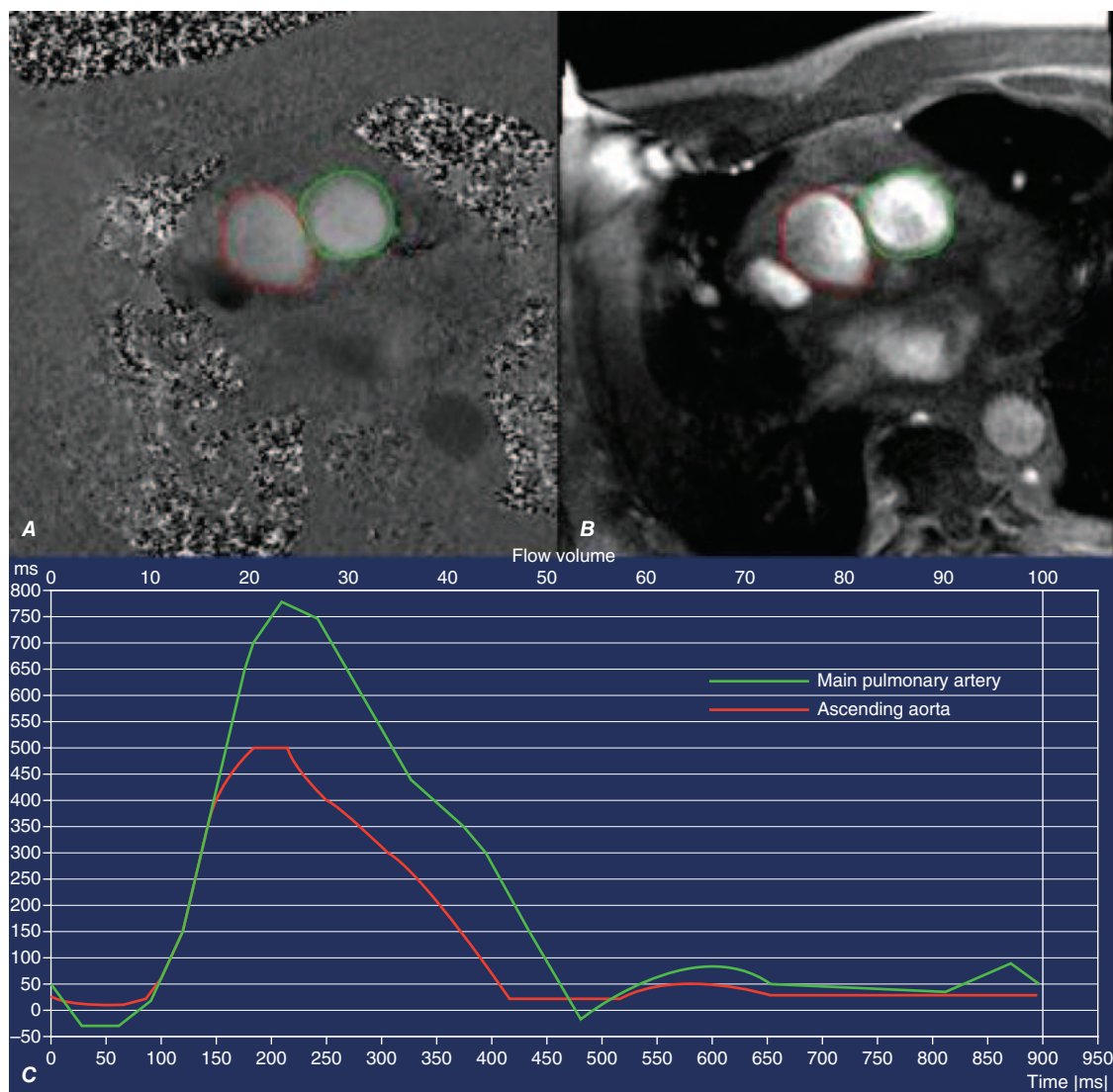


FIGURE 248-41 **A** and **B** are phase contrast images that display blood flow (phase images on **A**) and anatomy (structural images on **B**) of the aorta (red) and pulmonary artery (green). **C** demonstrates the flow curves of the aorta (red) and the pulmonary artery (green). Note that the total flow (area under the curve) was substantially higher in the pulmonary artery than the aorta, indicative of a marked elevated pulmonary-to-systemic shunt ratio, as a result of the partial anomalous pulmonary venous return that drained into the superior vena cava.

FURTHER READING

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VIDEO 248-1 Cine steady-state free precession (SSFP) imaging (left) in short axis in a patient who had a large anterior myocardial infarction. Only one cut of a stack of short axis is shown. This method allows quantification of left ventricular (LV) and right ventricular (RV) volumes in diastole and systole and calculation of the LV ejection fraction, stroke volumes, and cardiac output (a product of LV stroke volume and heart rate). Note that in this case there is anterior and anteroseptal akinesia (lack of systolic wall thickening, as shown by the left cine movie, red arrows) matching by a near-transmural myocardial infarction as seen by the matching late gadolinium enhancement (LGE) image (right picture, white arrows).

VIDEO 248-2 This is cine cardiac magnetic resonance (CMR) imaging of a patient in the long-axis four-chamber view. Note that the basal aspect of the right ventricular (RV) free wall is thickened, aneurysmal, and akinetic (red arrows). The

global RV systolic function is mildly reduced, and the RV is dilated. CMR can image the RV using tomographic views and can quantify the RV volumes and ejection fraction volumetrically. This is a patient who presented with syncopal spells and inducible ventricular tachycardia on subsequent workup. He was diagnosed to have arrhythmogenic right ventricular dysplasia.

VIDEO 248-3 Exercise echocardiogram showing rest images on left and poststress images on right, with parasternal long-axis, upper panel, and apical four-chamber, lower panel, end-systolic frames. Following exercise, the distal septal/apical region becomes akinetic. A = upper left (UL); B = upper right (UR); C = lower left (LL); D = lower right (LR).

VIDEO 248-4 The video shows cardiac magnetic resonance (CMR) myocardial perfusion imaging during vasodilating stress, in three parallel short-axis views. A bolus of gadolinium contrast was injected intravenously while rapid imaging acquisition occurred. The contrast enhances the right ventricle first, then travels through the pulmonary circulation, enters the left ventricle (LV), and then perfuses the LV myocardium. Myocardial perfusion defects with this technique show as black subendocardial rims, reflecting lack of contrast accumulation due to ischemia and/or scar. In this case, the anterior wall has a severe perfusion defect (red arrow). **Figure 248-14** shows the late gadolinium enhancement (LGE) image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

VIDEO 248-5 A 60-year-old female presented with intermittent chest pain of 3 days in duration but was pain-free at the time of assessment in the emergency room. Admission electrocardiogram (ECG) demonstrated T-wave inversion in the anterior

precordial lead, but cardiac enzymes were normal. A resting cardiac magnetic resonance (CMR) study reviewed a large area of anteroseptal hypokinesia (*left picture*, region of hypokinesia shown by the *red arrows*), matching with a large resting perfusion defect (*middle picture*, perfusion defect shown by the *blue arrows*). Late gadolinium enhancement (LGE) imaging (*right picture*), however, did not show any enhancement to indicate any infarction in the anteroseptal wall, suggesting that the hypocontractile and hypoperfused anteroseptal wall was viable. Urgent coronary angiography demonstrated an acute thrombus in the mid left anterior descending coronary artery, which required coronary stenting. This case represents an example of acute coronary syndrome with hibernating but viable myocardium in the anteroseptal wall. The anteroseptal wall recovered contractile function when reassessed 6 months later.

VIDEO 248-6 A patient with severe aortic regurgitation quantified by cardiac magnetic resonance (CMR). Notice the dark flow jet during diastolic across the aortic valve. For quantitation of the aortic regurgitation severity, a cross-sectional cut was made just below the aortic valve, perpendicular to the aortic regurgitation jet, using phase contrast flow imaging. Apart from aortic regurgitation fraction and volume, CMR also can volumetrically quantify ventricular sizes and dimensions of the aorta, which are useful in monitoring patients with aortic valve diseases.

VIDEO 248-7 These are T2* images of the heart (*left panel*) and the liver (*right panel*) of a patient who has hemochromatosis. Note that iron and the liver are markedly darkened in these movies, indicating high load of iron in the heart muscle and liver. The rate of signal reduction (decay) in the myocardium and liver can be calculated as T2* value expressed in milliseconds. In this case, the T2* was at 10 ms. T2* <20 ms in patients with cardiomyopathy has been shown to indicate iron toxicity as the etiology of the cardiomyopathy, and it carries prognostic value for such patients at risk of cardiac iron toxicity.

VIDEO 248-8 This video shows the heart in long and short axis. Note the large atria, thickened pericardium, and extensive pericardial adhesions. Given the extensive pericardial adhesions, there is little shearing motion of the ventricles against the parietal pericardium.

VIDEO 248-9 This video shows the heart in long axis with a 4-chamber view. The steady-state free precession (bright-blood) cine show the early diastolic filling bounce of the apical interventricular septum due to constrictive physiology.

249

Diagnostic Cardiac Catheterization and Coronary Angiography

Jane A. Leopold, Ajar Kochar

Diagnostic cardiac catheterization and coronary angiography are considered the gold standard in the assessment of the anatomy and physiology of the heart and its associated vasculature. In 1929, Forssmann demonstrated the feasibility of cardiac catheterization in humans when he passed a urological catheter from a vein in his arm to his right atrium and documented the catheter's position in the heart by x-ray. In the 1940s, Cournand and Richards applied this technique to patients with cardiovascular disease to evaluate cardiac function. These three physicians were awarded the Nobel Prize in 1956. In 1958, Sones inadvertently performed the first selective coronary angiography when a catheter in the left ventricle slipped back across the aortic valve, engaged the right coronary artery, and power-injected 40 mL of contrast down the vessel. The resulting angiogram provided superb anatomic detail of the artery, and the patient suffered no adverse effects. Sones went on to develop selective coronary catheters, which were modified further by Judkins, who developed preformed catheters and allowed coronary artery angiography to gain widespread use as a diagnostic tool. In the

United States, cardiac catheterization is the second most common operative procedure, with more than 1.0 million procedures performed annually.

CARDIAC CATHETERIZATION

■ INDICATIONS, RISKS, AND PREPROCEDURE MANAGEMENT

Cardiac catheterization and coronary angiography are indicated to evaluate the extent and severity of cardiac disease in symptomatic patients and to determine if medical, surgical, or catheter-based interventions are warranted ([Table 249-1](#)). They are also used to exclude

TABLE 249-1 Indications for Cardiac Catheterization and Coronary Angiography

Asymptomatic or Symptomatic Coronary Artery Disease

High risk for adverse outcome based on noninvasive testing
Sudden cardiac death
Sustained (>30 s) monomorphic ventricular tachycardia
Nonsustained (<30 s) polymorphic ventricular tachycardia

Symptomatic Coronary Artery Disease

Canadian Cardiology Society Class II, III, or IV stable angina on medical therapy
Acute coronary syndrome (unstable angina and non-ST-segment elevation myocardial infarction)
Chest-pain syndrome of unclear etiology and equivocal findings on noninvasive tests

Acute Myocardial Infarction

Reperfusion with primary percutaneous coronary intervention
Persistent or recurrent ischemia
Pulmonary edema and/or reduced ejection fraction
Cardiogenic shock or hemodynamic instability
Risk stratification or positive stress test after acute myocardial infarction
Mechanical complications—mitral regurgitation, ventricular septal defect

Valvular Heart Disease

Suspected severe valve disease in symptomatic patients—dyspnea, angina, heart failure, syncope
Infective endocarditis with need for cardiac surgery
Asymptomatic patients with aortic regurgitation and cardiac enlargement or ↓ ejection fraction
Prior to cardiac surgery or transcatheter aortic valve replacement or other percutaneous valvular interventions in patients with suspected coronary artery disease

Congestive Heart Failure

New-onset angina or suspected undiagnosed coronary artery disease
New-onset cardiomyopathy of uncertain cause or suspected to be due to coronary artery disease

Congenital Heart Disease

Prior to surgical correction or percutaneous interventions, when symptoms or noninvasive testing suggests coronary disease
Suspicion for congenital coronary anomalies

Pericardial Disease

Symptomatic patients with suspected cardiac tamponade or constrictive pericarditis

Cardiac Transplantation

Preoperative and postsurgical evaluation

Other Conditions

Hypertrophic cardiomyopathy with angina
Diseases of the aorta when knowledge of coronary artery involvement is necessary for management
Pulmonary hypertension
Unexplained dyspnea

severe disease in symptomatic patients with equivocal findings on non-invasive studies and in patients with chest-pain syndromes of unclear etiology for whom a definitive diagnosis is necessary for management. Cardiac catheterization is not mandatory prior to cardiac surgery in some younger patients who have uncomplicated congenital or valvular heart disease that is well defined by noninvasive imaging and who do not have symptoms or risk factors that suggest concomitant coronary artery disease.

The risks associated with elective cardiac catheterization are relatively low, with a reported risk of <0.1% for myocardial infarction, 0.01% for stroke, and 0.05% for death. For elective and emergent procedures, the in-hospital mortality is 1.4%. These risks increase substantially if the catheterization is performed emergently, during acute myocardial infarction, or in hemodynamically unstable patients. Additional risks of the procedure include tachy- or bradyarrhythmias that require countershock, temporary pacing or pharmacologic therapy, acute renal failure leading to transient or permanent dialysis, air embolus, hemodynamic compromise, acute pulmonary edema, aortic dissection or other peripheral vascular complications that necessitate surgical repair or percutaneous intervention, and significant access-site bleeding. Of these risks, vascular access-site bleeding is the most common complication, occurring in 1.5–2.0% of patients, with major bleeding events associated with a worse short- and long-term outcome. These vascular access site bleeding complications are less common with the radial approach as compared with the femoral access site.

In patients who understand and accept the risks associated with cardiac catheterization, there are no absolute contraindications when the procedure is performed in anticipation of a life-saving intervention. Relative contraindications for elective procedures do, however, exist; these include decompensated congestive heart failure; acute renal failure; severe chronic renal insufficiency, unless dialysis is planned; bacteremia; acute stroke; active gastrointestinal bleeding; excessive anticoagulation or recent lytic administration; severe, uncorrected electrolyte abnormalities; a history of an anaphylactic/anaphylactoid reaction to iodinated contrast agents without premedication; and a history of allergy/anaphylaxis/bronchospasm to aspirin in patients for whom progression to a percutaneous coronary intervention is likely and aspirin desensitization has not been performed. For right heart catheterization, contraindications include right heart tumor, endocarditis, thrombus, or clot in transit.

Contrast allergy and contrast-induced acute kidney injury merit further consideration because these adverse events may occur in otherwise healthy individuals and prophylactic measures exist to reduce risk. Allergic reactions to contrast agents occur in <5% of cases, with severe anaphylactoid (clinically indistinguishable from anaphylaxis, but not mediated by an IgE mechanism) reactions occurring in 0.1–0.2% of patients. Mild reactions manifest as nausea, vomiting, and urticaria, while severe anaphylactoid reactions lead to hypotensive shock, pulmonary edema, and cardiorespiratory arrest. Patients with a history of significant contrast allergy should be premedicated prior to planned coronary angiography with corticosteroids (prednisone 50 mg orally 13, 7, and 1 hour prior to the procedure) and antihistamines (H_1 -blockers), and studies performed with nonionic, low-osmolar contrast agents that have a lower reported rate of allergic reactions.

Contrast-induced acute kidney injury, defined as an increase in creatinine >0.5 mg/dL or 25% above baseline that occurs 48–72 h after contrast administration, occurs in ~2–7% of patients, with rates of 20–30% reported in high-risk patients. Risk factors for contrast-induced kidney injury are diabetes mellitus, congestive heart failure, chronic kidney disease, anemia, older age, and ST-segment elevation myocardial infarction. Dialysis is required in 0.3–0.7% of patients and is associated with a fivefold increase in in-hospital mortality. For all patients, adequate intravascular volume expansion with intravenous 0.9% saline (1.0–1.5 mL/kg per hour) for 3–12 h before and continued 6–24 h after the procedure limits the risk of contrast-induced acute kidney injury by >50%. Other strategies to decrease risk include the administration of sodium bicarbonate (3 mL/kg per hour) 1 h before and 6 h after the procedure (similar outcome to saline infusion); use of low- or iso-osmolar contrast agents; and limiting the volume

of contrast to <50 mL per procedure. Diabetic patients treated with metformin should stop the drug 24 h prior to the procedure and not restart until 48 h after contrast administration to limit the associated risk of lactic acidosis.

Cardiac catheterization is performed after the patient has fasted for 6 h and has received intravenous conscious sedation to remain awake but sedated during the procedure. Diabetic patients who have a tendency to develop hypoglycemia should hold oral hypoglycemic medications. All patients with suspected coronary artery disease are pretreated with 325 mg of aspirin. In patients in whom the procedure is likely to progress to a percutaneous coronary intervention, an additional P2Y₁₂ antiplatelet inhibitor agent should be started: clopidogrel (600-mg loading dose and 75 mg daily), prasugrel (60-mg loading dose and 10 mg daily), or ticagrelor (180-mg loading dose and 90 mg twice daily). Prasugrel should not be selected for individuals with prior stroke or transient ischemic attack and is not recommended for patients 75 years of age or older. Ticagrelor should not be chosen for patients with bradycardia; additionally, up to 10% of patients treated with ticagrelor may experience dyspnea. For those patients who will be treated with an oral anticoagulant after the procedure, clopidogrel is the antiplatelet agent of choice. Intravenous cangrelor may be used for patients who are unable to tolerate an oral P2Y₁₂ inhibitor medication. Warfarin is held starting 2–3 days prior to the catheterization to allow the international normalized ratio (INR) to fall to <1.8 and limit access-site bleeding complications. For patients at high risk of thrombotic complications (mechanical heart valve, ventricular assist device), a heparin bridge may be necessary. The direct oral anticoagulants (DOACs) should be stopped 24–48 h prior to the test. Cardiac catheterization is a sterile procedure, so antibiotic prophylaxis is not required.

■ TECHNIQUE

Cardiac catheterization and coronary angiography provide a detailed hemodynamic and anatomic assessment of the heart and coronary arteries. The selection of procedures is dependent on the patient's symptoms and clinical condition, with some direction provided by noninvasive studies.

Vascular Access Cardiac catheterization procedures are performed using a percutaneous technique to enter the femoral, radial, or ulnar artery and femoral, brachial, or internal jugular vein as the access sites for left and right heart catheterization, respectively. A flexible sheath is inserted into the vessel over a guidewire, allowing diagnostic catheters to be introduced into the vessel and advanced toward the heart using fluoroscopic guidance. The radial artery (or rarely the ulnar or brachial artery) access site is advantageous in patients with peripheral arterial disease that involves the abdominal aorta, iliac, or femoral vessels; severe iliac artery tortuosity, morbid obesity, or preference for early postprocedure ambulation. Use of radial artery access is the preferred access route due to a lower rate of access-site bleeding complications and improved patient comfort. The femoral artery should be accessed using a micro-puncture needle with ultrasound guidance to ensure that the insertion site is above the bifurcation of the profunda femoris and superficial femoral artery and below the inferior epigastric artery. Femoral artery access outside this zone increases the risk of retroperitoneal hemorrhage, pseudoaneurysm formation, and/or arteriovenous fistula. Complications associated with radial artery access include severe radial vasospasm that may result in device entrapment, forearm hematoma, and rarely, compartment syndrome. The internal jugular or antecubital veins serve as the preferred access sites to the right heart when the patient has an inferior vena cava filter in place or requires prolonged hemodynamic monitoring.

Right Heart Catheterization This procedure measures pressures in the right heart and pulmonary artery. Right heart catheterization is no longer a routine part of diagnostic cardiac catheterization, but it is reasonable in patients with unexplained dyspnea, pulmonary hypertension, valvular heart disease, pericardial disease, right and/or left ventricular dysfunction, congenital heart disease, and suspected intracardiac shunts. Right heart catheterization most commonly uses a balloon-tipped flotation catheter that is advanced sequentially to the right atrium, right ventricle, pulmonary artery, and pulmonary

wedge position (as a surrogate for left atrial pressure) using fluoroscopic guidance; in each cardiac chamber, pressure is measured and blood samples are obtained for oxygen saturation analysis to screen for intracardiac shunts and calculate a cardiac output.

Left Heart Catheterization This procedure measures pressures in the left heart as a determinant of left ventricular performance. With the aid of fluoroscopy, a catheter is guided to the ascending aorta and across the aortic valve into the left ventricle to provide a direct measure of left ventricular pressure. In patients with a tilting-disc prosthetic aortic valve, crossing the valve with a catheter is contraindicated, and the left heart may be accessed via a transseptal technique from the right atrium using a needle-tipped catheter to puncture the atrial septum at the fossa ovalis. Once the catheter crosses from the right to the left atrium, it can be advanced across the mitral valve to the left ventricle. This technique is also used for mitral valvuloplasty. Heparin is given for prolonged procedures to limit the risk of stroke from embolism of clots that may form on the catheter. For patients with heparin-induced thrombocytopenia, the direct thrombin inhibitors bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of the procedure) or argatroban (350 µg/kg bolus, 15 µg/kg per min for the duration of the procedure) may be used.

HEMODYNAMICS

A comprehensive hemodynamic assessment involves obtaining pressure measurements in the right and left heart and peripheral arterial system and determining the cardiac output (Table 249-2). The shape and magnitude of the pressure waveforms provide important diagnostic information; an example of normal pressure tracings is shown in Fig. 249-1. In the absence of valvular heart disease, the atria and ventricles are “one chamber” during diastole when the tricuspid and mitral valves are open, whereas in systole, when the pulmonary

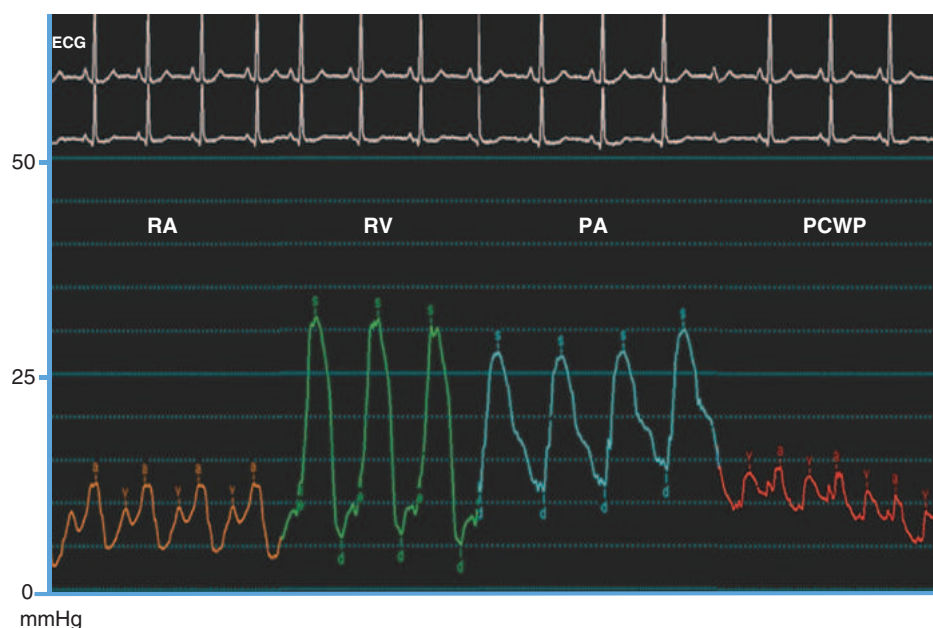


FIGURE 249-1 Normal hemodynamic waveforms recorded during right heart catheterization. Atrial pressure tracings have a characteristic “a” wave that reflects atrial contraction and a “v” wave that reflects pressure changes in the atrium during ventricular systole. Ventricular pressure tracings have a low-pressure diastolic filling period and a sharp rise in pressure that occurs during ventricular systole. d, diastole; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle; s, systole.

and aortic valves are open, the ventricles and their respective outflow tracts are considered “one chamber.” These concepts form the basis by which hemodynamic measurements are used to assess valvular stenosis. When aortic stenosis is present, there is a systolic pressure gradient between the left ventricle and the aorta; when mitral stenosis is present, there is a diastolic pressure gradient between the pulmonary capillary wedge (left atrial) pressure and the left ventricle (Fig. 249-2). Hemodynamic measurements also discriminate between aortic stenosis and hypertrophic obstructive cardiomyopathy where the asymmetrically hypertrophied septum creates a dynamic intraventricular pressure gradient during ventricular systole. The magnitude of this obstruction is measured using an end-hole catheter positioned at the left ventricular apex that is pulled back while recording pressure; once the catheter has passed the septal obstruction and is positioned in the apex of the left ventricle, a gradient can be measured between the left ventricular apex and the aorta. Hypertrophic obstructive cardiomyopathy is confirmed by the Brockenhough-Braunwald sign: following a premature ventricular contraction, there is an increase in the left ventricular–aorta pressure gradient with a simultaneous decrease in the aortic pulse pressure. The finding of a decrease in pulse pressure is absent in aortic stenosis.

Regurgitant valvular lesions increase volume (and pressure) in the “receiving” cardiac chamber. In severe mitral and tricuspid regurgitation, the increase in blood flow to the atria takes place during ventricular systole, leading to an increase in the v wave (often two times greater than the mean pressure). The size of the v wave is a measure of the compliance of the left atrium but is not a reliable measure of the severity of the mitral regurgitation. Severe aortic regurgitation leads to a decrease in aortic diastolic pressure with a concomitant rise in left ventricular end-diastolic pressure, resulting in equalization of pressures between the two chambers at end diastole.

Hemodynamic measurements are also used to differentiate between cardiac tamponade, constrictive pericarditis, and restrictive cardiomyopathy (Table 249-3). In cardiac tamponade, right atrial pressure is increased with a decreased or absent “y” descent, indicative of impaired right atrial emptying in diastole, and there is diastolic equalization of pressures in all cardiac chambers. In constrictive pericarditis, right atrial pressure is elevated with a prominent “y” descent, indicating rapid filling of the right ventricle during early diastole. A diastolic dip and plateau, or “square root sign,” in the ventricular waveforms due to an abrupt halt in ventricular filling during diastole, elevated right

TABLE 249-2 Normal Values for Hemodynamic Measurements

Pressures (mmHg)	
Right atrium (mean)	1–8
Right ventricle	
Peak systolic/end diastolic	15–30/1–8
Pulmonary artery	
Peak systolic/end diastolic	15–30/4–12
Mean	9–19
Pulmonary capillary wedge (mean)	4–12
Left atrium (mean)	4–12
Left ventricle	
Peak systolic/end diastolic	90–129/5–12
Aorta	
Peak systolic/end diastolic	90–129/60–79
Mean	70–100
Resistances ([dyn-s]/cm ⁵)	
Systemic vascular resistance	900–1400
Pulmonary vascular resistance	40–120
Oxygen Consumption Index ([L-min]/m ²)	
Arteriovenous oxygen difference (vol %)	3.5–4.8
Cardiac index ([L-min]/m ²)	2.8–4.2

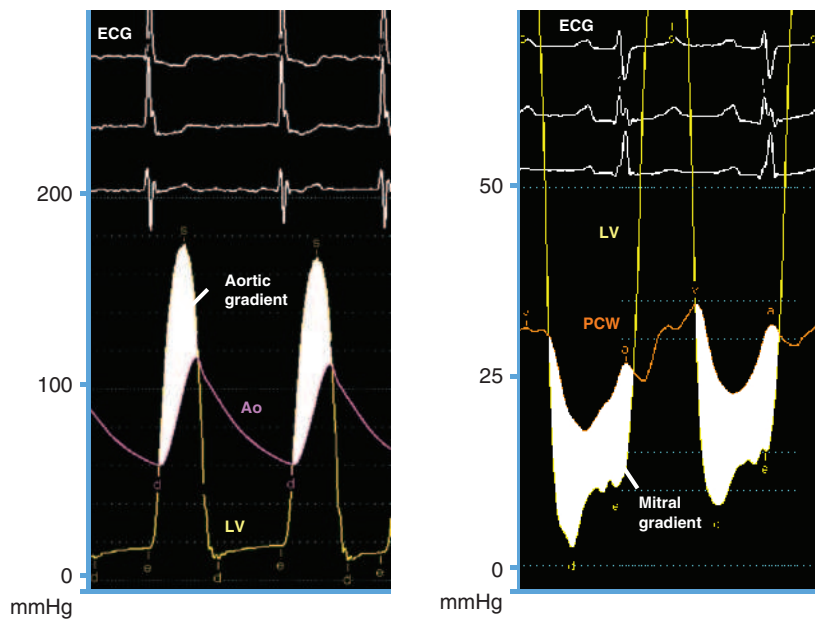


FIGURE 249-2 Severe aortic and mitral stenosis. Simultaneous recording of left ventricular (LV) and aortic (Ao) pressure tracings demonstrates a 62-mmHg mean systolic gradient (shaded area) that corresponds to an aortic valve area of 0.6 cm² (left). Simultaneous recording of LV and pulmonary capillary wedge (PCW) pressure tracings reveals a 14-mmHg mean diastolic gradient (shaded area) that is consistent with critical mitral stenosis (mitral valve area = 0.5 cm²). d, diastole; e, end diastole; s, systole.

ventricular and pulmonary artery pressures, and discordant pressure changes in the right and left ventricles with inspiration (right ventricular systolic pressure increases while left ventricular systolic pressure decreases) are observed. In the absence of constriction, the two ventricular pressures are concordant. The latter hemodynamic phenomenon is the most specific for constriction. Restrictive cardiomyopathy may be distinguished from constrictive pericarditis by a marked increase in right ventricular and pulmonary artery systolic pressures (usually >60 mmHg), a separation of the left and right ventricular diastolic pressures by >5 mmHg (at baseline or with acute volume loading), and concordant changes in left and right ventricular diastolic filling pressures with inspiration (both increase).

Cardiac Output Cardiac output is measured by the Fick method or the thermodilution technique. Typically, the Fick method and thermodilution technique are both performed during cardiac catheterization, although the Fick method is considered more reliable in the presence

of tricuspid regurgitation and in low-output states. The Fick method uses oxygen as the indicator substance and is based on the principle that the amount of a substance taken up or released by an organ (oxygen consumption) is equal to the product of its blood flow (cardiac output) and the difference in the concentration of the substance in the arterial and venous circulation (arterial-venous oxygen difference). Thus, the formula for calculating the Fick cardiac output is:

$$\text{Cardiac output (L/min)} = \frac{\text{oxygen consumption [mL/min]}}{\text{arterial-venous oxygen difference [mL/L]}}$$

If oxygen consumption is not measured directly, then it is estimated as 125 mL oxygen/minute × body surface area, and the arterial-venous oxygen difference is determined by first calculating the oxygen-carrying capacity of blood (hemoglobin [g/100 mL] × 1.36 [mL oxygen/g hemoglobin] × 10) and multiplying this product by the fractional oxygen saturation. The indicator dilution method measures the concentration of a substance that is injected proximally, adequately mixes with blood, and is then sampled distally. In contemporary practice, thermodilution cardiac outputs are measured using temperature as the indicator. Measurements are made with a thermistor-tipped catheter that detects temperature deviations in the pulmonary artery after the injection of 10 mL of room-temperature normal saline into the right atrium.

Vascular Resistance Resistance across the systemic and pulmonary circulations is calculated by extrapolating from Ohm's law of electrical resistance and is equal to the mean pressure gradient divided by the mean flow (cardiac output). Therefore, systemic vascular resistance is [(mean aortic pressure – mean right atrial pressure)/cardiac output] multiplied by 80 to convert the resistance from Wood units to dyn·s·cm⁻⁵. Similarly, the pulmonary vascular resistance is [(mean pulmonary artery – mean pulmonary capillary wedge pressure)/cardiac output] × 80. Pulmonary vascular resistance is lowered by oxygen, nitroprusside, calcium channel blockers, prostacyclin infusions, and inhaled nitric oxide; these therapies may be administered during catheterization to determine if increased pulmonary vascular resistance is fixed or reversible.

Valve Area Hemodynamic data may also be used to calculate the valve area using the Gorlin formula that equates the area to the flow

TABLE 249-3 Hemodynamic Findings in Tamponade, Constrictive Pericarditis, and Restrictive Cardiomyopathy

	CARDIAC TAMPONADE	CONSTRUCTIVE PERICARDITIS	EFFUSIVE-CONSTRUCTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY
Pericardial pressure	↑	↑	↑	Normal
Right atrium pressure	↑	↑	↑ (Fails to decrease by 50% or to <10 mmHg after pericardiocentesis)	↑
Right atrium pressure waveform	Prominent "x" descent Diminished or absent "y" descent	Prominent "x" descent Prominent "y" descent	Prominent "x" descent "y" descent less prominent than expected	Prominent "y" descent
Right ventricle systolic pressure	<50 mmHg	<50 mmHg	<50 mmHg	>60 mmHg
Right ventricle end-diastolic pressure	Equals left ventricular end-diastolic pressure within 5 mmHg	>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	<1/3 right ventricular systolic pressure Less than left ventricular end-diastolic pressure by ≥5 mmHg
Right ventricle pressure waveform		Dip and plateau or "square root" sign	Dip and plateau or "square root" sign	Dip and plateau or "square root" sign
Right ventricle–left ventricle systolic pressure relationship with inspiration	Discordant	Discordant	Discordant	Concordant

across the valve divided by the pressure gradient between the cardiac chambers surrounding the valve. The formula for the assessment of valve area is: $\text{Area} = (\text{cardiac output [cm}^3/\text{min}]/[\text{systolic ejection period or diastolic filling period}][\text{heart rate}])/44.3 C \times \text{square root of the pressure gradient}$, where $C = 1$ for aortic valve and 0.85 for the mitral valve. A valve area of $<1.0 \text{ cm}^2$ and a mean gradient of $>40 \text{ mmHg}$ indicate severe aortic stenosis, while a valve area of $<1.5 \text{ cm}^2$ and a mean gradient $>5\text{--}10 \text{ mmHg}$ are consistent with moderate-to-severe mitral stenosis; in symptomatic patients with a mitral valve area $>1.5 \text{ cm}^2$, a mean gradient $>15 \text{ mmHg}$, pulmonary artery pressure $>60 \text{ mmHg}$, or a pulmonary artery wedge pressure $>25 \text{ mmHg}$ after exercise is also considered significant and may warrant intervention. The modified Hakki formula has also been used to estimate aortic valve area. This formula calculates the valve area as the cardiac output (L/min) divided by the square root of the pressure gradient. Aortic valve area calculations based on the Gorlin formula are flow-dependent, and therefore, for patients with low cardiac outputs, it is imperative to determine if a decreased valve area actually reflects a fixed stenosis or is overestimated by a low cardiac output and stroke volume that is insufficient to open the valve leaflets fully. In these instances, cautious hemodynamic manipulation using dobutamine to increase the cardiac output and recalculation of the aortic valve area may be necessary.

Intracardiac Shunts In patients with congenital heart disease or unexplained hypoxemia, detection, localization, and quantification of the intracardiac shunt should be evaluated. A shunt should be suspected when there is unexplained arterial desaturation or increased oxygen saturation of venous blood. A “step up” or increase in oxygen content indicates the presence of a left-to-right shunt while a “step down” indicates a right-to-left shunt. The shunt is localized by detecting a difference in oxygen saturation levels of $5\text{--}7\%$ between adjacent cardiac chambers. The severity of the shunt is determined by the ratio of pulmonary blood flow (Q_p) to the systemic blood flow (Q_s), or $Q_p/Q_s = ([\text{systemic arterial oxygen content} - \text{mixed venous oxygen content}]/[\text{pulmonary vein oxygen content} - \text{pulmonary artery oxygen content}])$. For an atrial septal defect, a shunt ratio of 1.5 is considered significant and factored with other clinical variables to determine the need for intervention. When a congenital ventricular septal defect is present, a shunt ratio of ≥ 1.5 with evidence of left ventricular volume overload is a strong indication for surgical correction.

■ VENTRICULOGRAPHY AND AORTOGRAPHY

Ventriculography to assess left ventricular function may be performed during cardiac catheterization. A pigtail catheter is advanced retrograde across the aortic valve into the left ventricle, and $30\text{--}45 \text{ mL}$ of contrast is power-injected to visualize the left ventricular chamber during the cardiac cycle. The ventriculogram is usually performed in the right anterior oblique projection to examine wall motion and mitral valve function. Normal wall motion is observed as symmetric contraction of all segments; hypokinetic segments have decreased contraction, akinetic segments do not contract, and dyskinetic segments appear to bulge paradoxically during systole (Fig. 249-3). Ventriculography may also reveal a left ventricular aneurysm, pseudoaneurysm, or diverticulum, or an apical ballooning pattern consistent with

takotsubo cardiomyopathy, and can also be used to assess mitral valve prolapse and the severity of mitral regurgitation. The degree of mitral regurgitation is estimated by comparing the density of contrast opacification of the left atrium with that of the left ventricle. Minimal contrast reflux into the left atrium is considered $1+$ mitral regurgitation, while contrast density in the left atrium that is greater than that in the left ventricle with reflux of contrast into the pulmonary veins within three beats defines $4+$ mitral regurgitation. When it takes more than three beats but fully fills the atrium, it is $3+$. Both $3+$ and $4+$ are considered severe regurgitation. Ventriculography performed in the left anterior oblique projection can be used to identify a ventricular septal defect. Calculation of the ventricular volumes in systole and diastole allows calculation of stroke volume and cardiac output.

Aortography in the cardiac catheterization laboratory visualizes abnormalities of the ascending aorta, including aneurysmal dilation and involvement of the great vessels, as well as dissection with compression of the true lumen by an intimal flap that separates the true and false lumina. Aortography can also be used to identify patent saphenous vein grafts that elude selective cannulation, identify shunts that involve the aorta such as a patent ductus arteriosus, evaluate the takeoff or proximal anatomy of the great vessels, and provide a qualitative assessment of aortic regurgitation using a $1\text{--}4+$ scale similar to that used for mitral regurgitation.

■ CINEFLUOROSCOPY OF PROSTHETIC MECHANICAL VALVES

Prosthetic valve leaflet dysfunction may occur as a result of thrombus or obstruction of leaflet excursion by pannus (Fig. 249-4). The incidence of prosthetic valve thrombosis in left-sided valves is $0.1\text{--}6.0\%$ per patient-year with differences in rates attributable to valve type, position, anticoagulation status, and left ventricular function. Prosthetic valve dysfunction should be suspected in patients with subtherapeutic anticoagulation with a low mean INR, a prothrombotic state, recent-onset heart failure, cardiogenic shock, cardiac arrest, thromboembolic

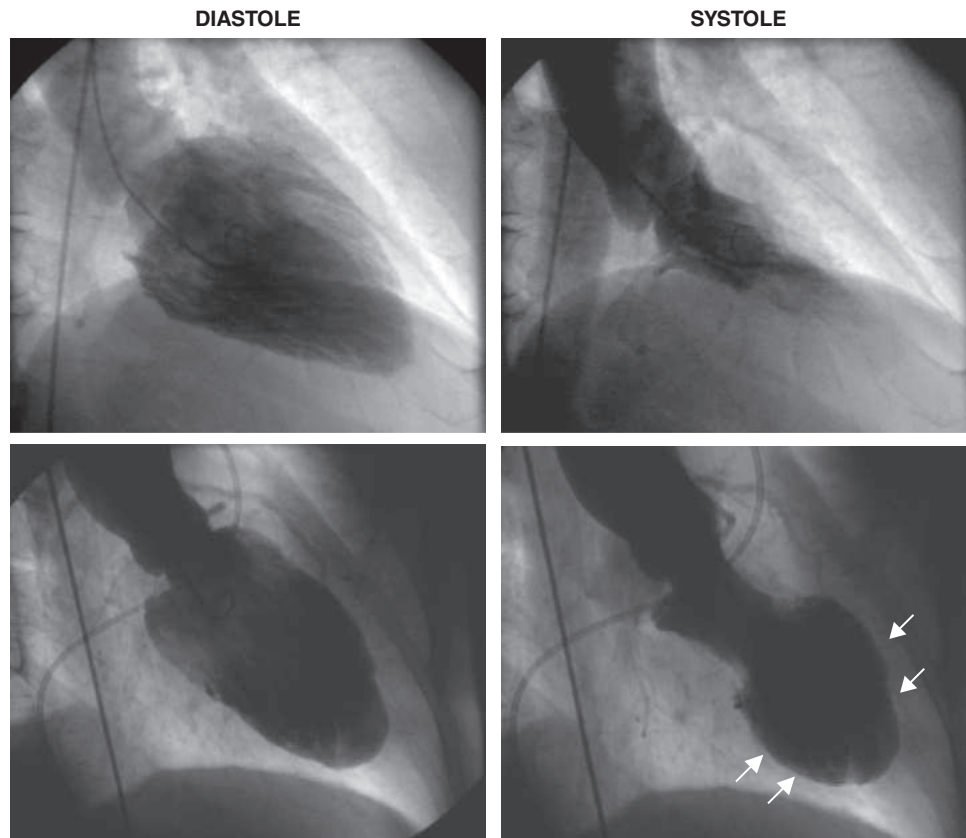


FIGURE 249-3 Left ventriculogram at end diastole (left) and end systole (right). In patients with normal left ventricular function, the ventriculogram reveals symmetric contraction of all walls (top). Patients with coronary artery disease may have wall motion abnormalities on ventriculography as seen in this 60-year-old male following a large anterior myocardial infarction. In systole, the anterior, apical, and inferior walls are akinetic (white arrows) (bottom).

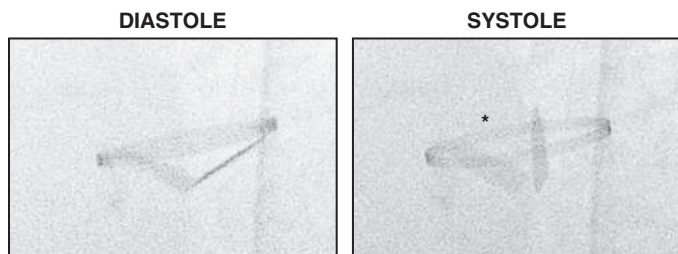


FIGURE 249-4 Cinefluoroscopic detection of mechanical valve leaflet dysfunction. Images of a bileaflet mechanical valve in the aortic position taken during diastole (left) and systole (right) show that one leaflet opens normally during systole while the other leaflet (below asterisk) remains immobile and fixed consistent with valve leaflet thrombosis.

event, or, in asymptomatic patients, an increasing gradient across the valve. Cinefluoroscopy visualizes the motion of mechanical valve leaflets, is noninvasive, is available in most centers, and can be performed rapidly with minimal radiation exposure. Prosthetic mechanical valves should be imaged *en face* and at a 90° angle over several cardiac cycles to document opening and closing of the valve leaflets as well as motion of the base ring. Each type of prosthetic valve has leaflet opening and closing angles that are reported by the manufacturer and can be used to determine if movement or closure of the valve leaflets is restricted, suggestive of mechanical obstruction.

CORONARY ANGIOGRAPHY

Selective coronary angiography is almost always performed during cardiac catheterization and is used to define the coronary anatomy and determine the extent of epicardial coronary artery and coronary artery bypass graft disease. Specially shaped coronary catheters are used to engage the left and right coronary ostia. Injection of radiopaque contrast agents by hand or automated contrast injector system creates a coronary “luminogram” that is recorded as radiographic images (cine angiography). Because the coronary arteries are three-dimensional objects that are in motion with the cardiac cycle, angiograms of the vessels using several different orthogonal projections are taken to best visualize the vessels without overlap or foreshortening.

The normal coronary anatomy is highly variable between individuals, but, in general, there are two coronary ostia and three major coronary vessels—the left anterior descending, the left circumflex, and the right coronary arteries with the left anterior descending and left circumflex arteries arising from the left main coronary artery (Fig. 249-5). When the right coronary artery is the origin of the atrioventricular nodal branch, the posterior descending artery, and the posterior lateral vessels, the circulation is defined as right dominant; this is found in ~85% of individuals. When these branches arise from the left circumflex artery, as occurs in ~5% of individuals, the circulation is defined as left dominant. The remaining ~10% of patients have a codominant circulation with the posterior descending vessel

arising from both the right coronary and the posterior lateral vessels from left coronary circulation. In some patients, a ramus intermedius branch arises directly from the left main coronary artery that trifurcates into the left anterior descending, ramus, and circumflex arteries; this finding is a normal variant. Coronary artery anomalies occur in 1–2% of patients, with separate ostia for the left anterior descending and left circumflex arteries (0.41%), ectopic origin of the right coronary artery from the left coronary sinus (0.92%), ectopic origin of the left circumflex artery from the right coronary sinus (0.67%), and fistulas between the coronary arteries and cardiac chambers or the pulmonary artery or vein (0.87%) being the most common. Certain anomalous coronary artery patterns increase the risk of sudden cardiac death, especially if the artery travels between the pulmonary artery and aorta.

Coronary angiography visualizes coronary artery stenoses as luminal narrowings on the cine angiogram. The degree of narrowing is referred to as the percent stenosis and is determined visually by comparing the most severely diseased segment with a proximal or distal “normal segment;” a stenosis >50% is considered significant (Fig. 249-6). Online quantitative coronary angiography can provide a more accurate assessment of the percent stenosis and lessen the tendency to overestimate lesion severity visually. The presence of a myocardial bridge, which most commonly involves the left anterior descending artery, may be mistaken for a significant stenosis; this occurs when a portion of the vessel dips below the epicardial surface into the myocardium and is subject to compressive forces during ventricular systole. The key to differentiating a myocardial bridge from a fixed stenosis is that the “stenosed” part of the vessel returns to normal during diastole. Coronary angiography may also reveal spontaneous coronary artery dissections that appear similar to a stenosis but tends to occur in an angiographically normal-appearing coronary artery; a linear dissection flap may be present. Coronary spasm appears similar to a fixed stenosis but resolves with the administration of intracoronary nitroglycerin. Coronary calcification is also seen during angiography prior to the injection of contrast agents. Collateral blood vessels may be seen traversing from one vessel to the distal vasculature of a severely stenosed or totally occluded vessel. Thrombolysis in myocardial infarction (TIMI) flow grade, a measure of the relative duration of time that it takes for contrast to opacify the coronary artery fully, may provide an additional clue to the degree of lesion severity, and the presence of TIMI grade 1 (minimal filling) or 2 (delayed filling) suggests that a severe coronary artery stenosis is present.

INTRAVASCULAR ULTRASOUND, OPTICAL COHERENCE TOMOGRAPHY, FRACTIONAL FLOW RESERVE, AND CORONARY FLOW RESERVE

During coronary angiography, intermediate stenoses (40–70%), indeterminate findings, or anatomic findings that are incongruous with the patient's symptoms may require further interrogation. In these cases, intravascular ultrasound (IVUS) provides a more accurate anatomic

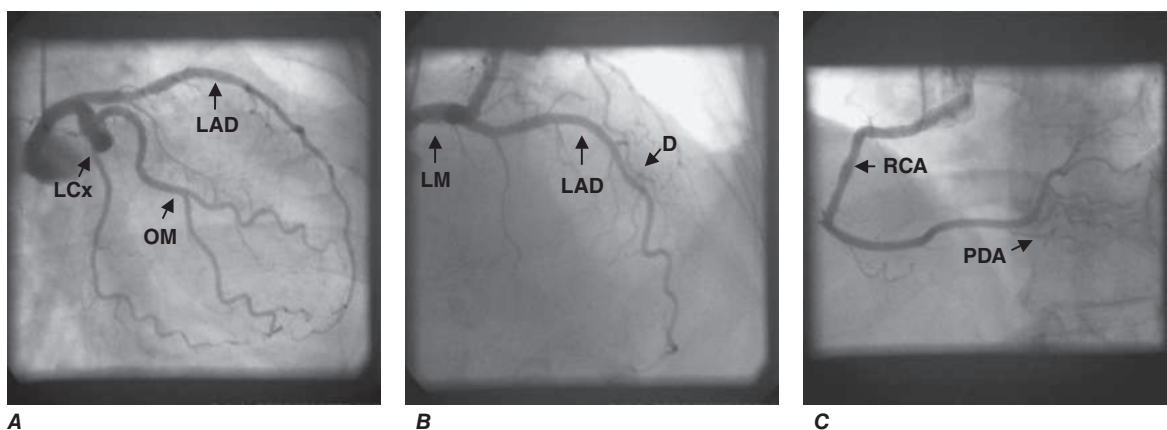


FIGURE 249-5 Normal coronary artery anatomy. **A.** Coronary angiogram showing the left circumflex (LCx) artery and its obtuse marginal (OM) branches. The left anterior descending (LAD) artery is also seen but may be foreshortened in this view. **B.** The LAD and its diagonal (D) branches are best seen in cranial views. In this angiogram, the left main (LM) coronary artery is also seen. **C.** The right coronary artery (RCA) gives off the posterior descending artery (PDA), so this is a right dominant circulation.

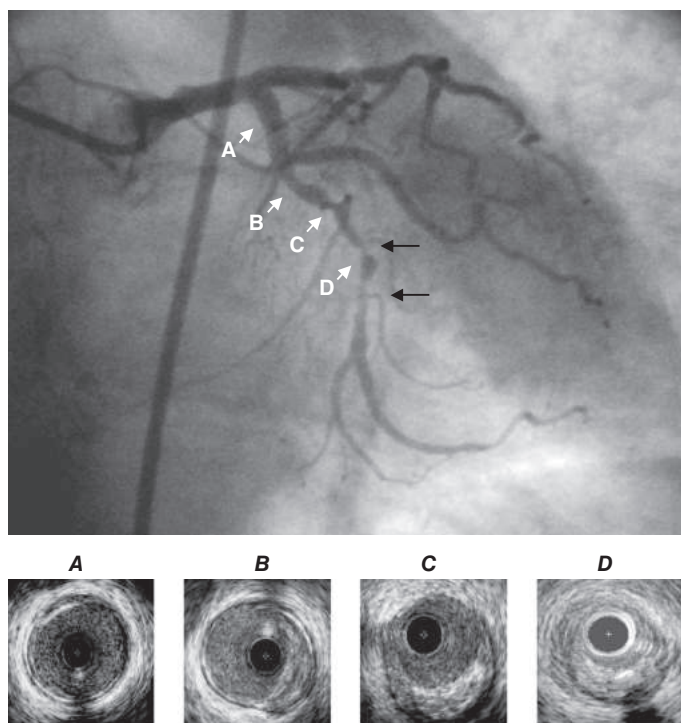


FIGURE 249-6 Coronary stenoses on cine angiogram and intravascular ultrasound. Significant stenoses in the coronary artery are seen as narrowings (black arrows) of the vessel. Intravascular ultrasound shows a normal segment of artery (A), areas with eccentric plaque (B, C), and near total obliteration of the lumen at the site of the significant stenosis (D). Note that the intravascular ultrasound catheter is present in the images as a black circle.

assessment of the coronary artery and the degree of coronary atherosclerosis (Fig. 249-6). IVUS is performed using a small flexible catheter with a transducer at its tip that is advanced into the coronary artery over a guidewire. Data from IVUS studies may be used to image atherosclerotic plaque precisely, determine luminal cross-sectional area, characterize plaque, including quantifying the arc and length of calcium, and measure vessel size. It is also used during or following percutaneous coronary intervention to assess the stenosis and determine the adequacy of the stent implantation procedure (stent expansion, apposition, geographic miss, or edge dissection). Optical coherence tomography (OCT) is a catheter-based imaging technique that uses near-infrared light to generate images with better spatial resolution than IVUS (10–15 microns vs 100–150 microns); however, the depth of field is smaller. The advantage of OCT imaging over IVUS lies in its ability to image characteristics of the atherosclerotic plaque (lipid, fibrous cap, plaque rupture or erosion, thrombus) with high definition and to assess coronary stent placement, apposition, and patency (Fig. 249-7).

Measurement of the fractional flow reserve provides a functional assessment of the stenosis and is more accurate in predicting long-term clinical outcome than imaging techniques. The fractional flow reserve is the ratio of the pressure in the coronary artery distal to the stenosis

divided by the pressure in the artery proximal to the stenosis at maximal vasodilation. Fractional flow reserve is measured using a coronary pressure-sensor guidewire at rest and at maximal hyperemia following the infusion of adenosine (Fig. 249-8). A fractional flow reserve of <0.80 indicates a hemodynamically significant stenosis that would benefit from intervention. The instantaneous wave-free ratio, which measures the gradient across the stenosis during the latter part of diastole, does not require the use of adenosine and may be preferred for some patients with asthma or documented allergy to adenosine. An instantaneous wave-free ratio of <0.89 is considered positive for ischemia. Resting gradients have also been shown to predict a significant stenosis.

Microvascular dysfunction can be evaluated by assessing coronary flow reserve, the ratio between coronary blood flow at maximal hyperemia and rest. Coronary flow reserve is measured using a Doppler wire- or pressure wire-based thermodilution technique in patients with unexplained chest pain or ischemia and no obstructive coronary artery disease. A coronary flow reserve <2.0 is considered abnormal. An index of microcirculatory resistance can also be calculated by multiplying the pressure wire thermodilution-derived mean transit time by the distal pressure. An index of microcirculatory resistance of <25 is considered normal. Studies have shown this derivative parameter to be an important predictor of outcome as well.

POSTPROCEDURE CARE

Once the procedure is completed, vascular access sheaths are removed. If the femoral approach is used, direct manual compression or vascular closure devices that immediately close the arteriotomy site with a staple/clip, collagen plug, or sutures are used to achieve hemostasis. These devices decrease the length of supine bed rest (from 6 h to 2–4 h) and improve patient satisfaction but have not been shown definitively to be superior to manual compression with respect to access-site complications. The overall risk of complications for vascular closure devices is low, but potential complications include infection, embolization, and limb ischemia. Vascular closure devices should be avoided in heavily diseased vessels where the risk of complications is increased. With radial-artery access, the sheath is removed and a plastic wristband with an air pillow is used to keep pressure on the access site while maintaining flow through the radial artery. Bed rest is needed for only 2 hours while the air in the wristband is released. When cardiac catheterization is performed as an elective outpatient procedure, the patient completes postprocedure bed rest in a monitored setting and is discharged home with instructions to liberalize fluids because contrast agents promote an osmotic diuresis, to avoid strenuous activity, and to observe the vascular access site for signs of complications. Overnight hospitalization may be required for high-risk patients with significant comorbidities, patients with complications occurring during the catheterization, or patients who have undergone a complicated percutaneous coronary intervention. Hypotension early after the procedure may be due to inadequate fluid replacement or retroperitoneal bleeding from the femoral access site. Patients who received >2 Gy of radiation during the procedure should be examined for signs of erythema. For patients who received higher doses (>5 Gy), clinical follow-up within 1 month to assess for skin injury is recommended.

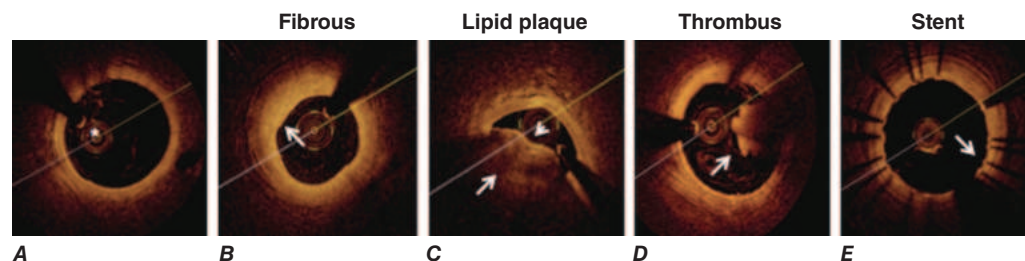


FIGURE 249-7 Optical coherence tomography imaging. A. The optical coherence tomography (OCT) catheter (*) in the lumen of a coronary artery with limited neointima formation. The intima is seen with high definition, but unlike intravascular ultrasound imaging, the vessel media and adventitia are not well visualized. B. A fibrous plaque (arrow) is characterized by a bright signal. C. A large, eccentric, lipid-rich plaque obscures part of the vessel lumen. Because lipid in the plaque absorbs light, the lipid-rich plaque appears as a dark area with irregular borders (arrow). The plaque is covered by a thin fibrous cap (arrowhead) typical of a vulnerable plaque. D. A thrombus (arrow) adherent to a ruptured plaque that is protruding into the vessel lumen. E. A coronary stent is that is well apposed to the vessel wall. The stent struts appear as short bright lines with dropout behind the struts (arrow).

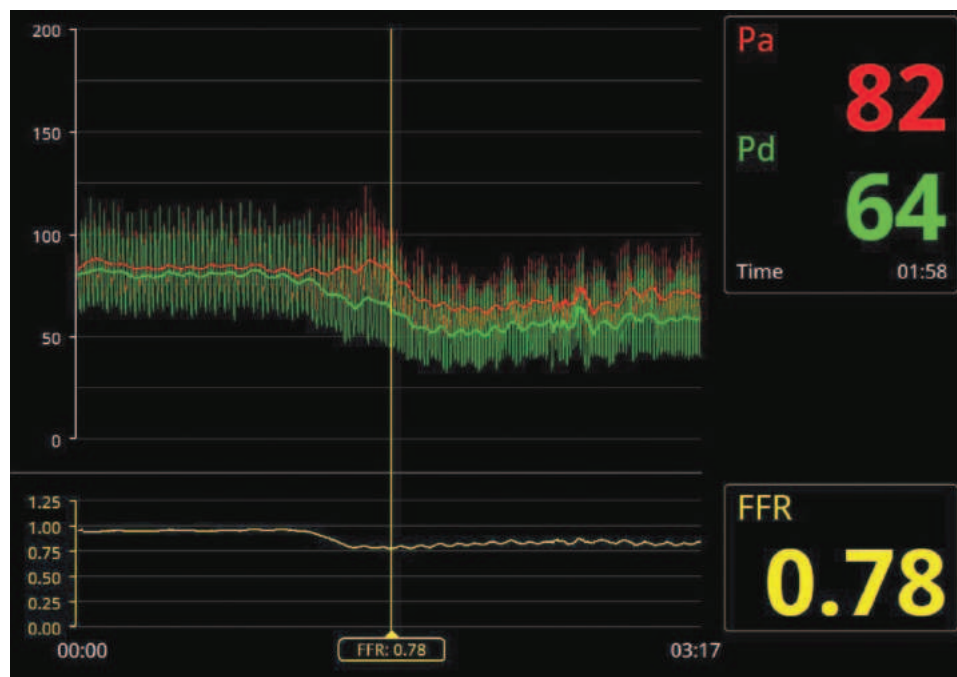


FIGURE 249-8 Fractional flow reserve. The fractional flow reserve is measured using a coronary pressure-sensor guidewire that measures the ratio of the pressure in the coronary artery distal to the stenosis (Pd, green) divided by the pressure in the artery proximal to the stenosis (Pa, red) at maximal hyperemia following the injection of adenosine. A fractional flow reserve of <0.80 indicates that revascularization would be beneficial.

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of the relationship between cardiac electrical potentials, mechanical cardiac function, and pathophysiology of cardiac arrhythmias. In the mid-twentieth century, the recording of cellular membrane currents enabled the understanding that the surface ECG represents the sum of cellular cardiac electrical activity. An understanding of cellular electrophysiology also ushered in the development of antiarrhythmic drugs utilized by cardiac electrophysiologists.

The modern era of clinical cardiac electrophysiology began with the first recordings of human intracardiac electrograms in the 1960s. Initially, invasive electrophysiology studies were limited to diagnostic tools. This included serial electrophysiologic testing to evaluate arrhythmia mechanisms and evaluate arrhythmia suppression by antiarrhythmic drugs, and programmed stimulation of the ventricle for risk stratification of sudden cardiac death. In the 1960s and 1970s, cardiac surgery was the only available invasive treatment for cardiac arrhythmias. The subsequent development of radiofrequency catheter ablation in the 1980s ushered in the era of interventional cardiac electrophysiology. In addition, with the development of implanted cardiac rhythm management devices including pacemakers and defibrillators, clinical cardiac electrophysiology became a distinct medical subspecialty. Developments in catheter ablation techniques, cardiac resynchronization and conduction system pacing, subcutaneous defibrillator implantation, leadless pacemaker implantation, left atrial appendage closure, and laser-assisted lead extraction have broadened the procedural aspects of the specialty over the past 30 years; however, the principles of arrhythmia patient management have remained the same.

Section 3 Disorders of Rhythm

250 Principles of Clinical Cardiac Electrophysiology

William H. Sauer, Bruce A. Koplan, Paul C. Zei

HISTORICAL PERSPECTIVE

Clinical cardiac electrophysiology is the subspecialty of cardiology that focuses on the study and management of heart rhythm disorders. The development of the modern surface electrocardiogram (ECG) by Willem Einthoven more than 100 years ago enabled an understanding

CELLULAR ELECTROPHYSIOLOGY

The cardiac action potential (AP) drives the electrophysiologic behavior of all cardiac myocytes. The AP is characterized morphologically by five distinct phases, termed phases 0–4, as shown in [Fig. 250-1](#). Moreover, as ventricular electrophysiologic activity accounts for the QRS and T complexes of the surface ECG, each AP phase in ventricular tissues corresponds to distinct phases in the surface ECG: Phase 0, the rapid upstroke, corresponds to the QRS deflection; phases 1–2 account for the ST segment; phase 3 accounts for the T wave; while phase 4 corresponds to the segment between the end of the T wave and the subsequent QRS deflection. In addition, the P wave corresponds to atrial depolarization, while the PR interval corresponds to the time between

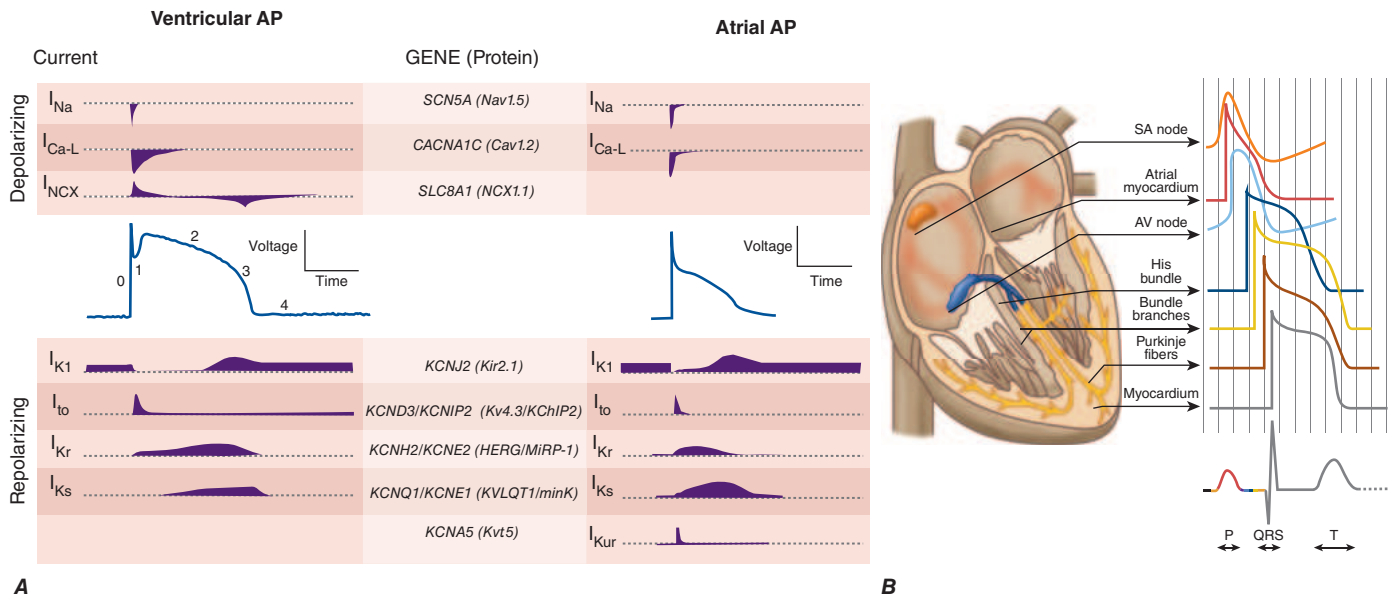


FIGURE 250-1 A. Cellular atrial and ventricular action potentials. Phases 0–4 are the rapid upstroke, early repolarization, plateau, late repolarization, and diastole, respectively. The ionic currents and their respective genes are shown above and below the action potentials. The currents that underlie the action potentials vary in atrial and ventricular myocytes. Potassium current (I_{K1}) is the principal current during phase 4 and determines the resting membrane potential of the myocyte. Sodium current generates the upstroke of the action potential (phase 0); activation of I_{to} with inactivation of the Na current inscribes early repolarization (phase 1). The plateau (phase 2) is generated by a balance of repolarizing potassium currents and depolarizing calcium current. Inactivation of the calcium current with persistent activation of potassium currents (predominantly I_{Kr} and I_{Ks}) causes phase 3 repolarization. Currents that result in membrane depolarization are grouped at the top of the figure above the action potentials, while repolarizing currents are shown below the action potentials. **B.** A surface electrocardiogram (ECG) representation of sinus rhythm is shown with respective intracardiac action potentials that are active during each phase of the ECG. Each cardiac conduction region's action potential is shown in the upper portion of the panel, with colors reflected in the ECG segment shown in the lower portion of the panel. Note that during the P wave, atrial depolarization is active. During the PR interval, the atrioventricular (AV) nodal, His, bundle branches, and Purkinje fibers are active (in sequence), although these action potentials are not discernible on the surface ECG. During the QRS interval, ventricular action potentials are active, with the QRS morphology most reflective of the sequence of ventricular tissue action potential activation. The ST segment is predominantly determined by the plateau phase 2 of the ventricular action potential. The T wave is determined largely by ventricular repolarization (phase 3), while the isoelectric segment is the result of the electrically neutral phase 4 of the ventricular action potential.

the initiation of atrial depolarization to the initiation of ventricular depolarization, comprised (typically) for the most part by the conduction time through the atrioventricular (AV) node.

AP morphologies are the result of the precise and carefully timed sequences of opening, closing, and inactivation of an array of membrane ion channels in response to cellular membrane potential changes, ligands that bind to the ion channel complex, or membrane stretch in a time-dependent fashion. The open ion channel allows flux of specific charged ions through a central pore, resulting in electrical (ionic) currents that drive the AP. The activity of different subsets of ion channels drives the different phases of the AP. Specific ionic currents that flux through an open channel are driven by the electrochemical gradient of that particular ion across the membrane, which in turn are driven by ion pumps or transporters/exchangers, which in turn are catalyzed by ATP (Fig. 250-2).

Ion channels are complex, multi-subunit transmembrane glycoproteins that contain a central pore that is selective for particular ionic species (selectivity); a “gating” apparatus that regulates the opening, closing, and inactivation apparatus; and often one or more regulatory subunits. Most channels gate in response to changes in membrane potential, a specific ligand, or mechanical deformation. The molecular underpinnings of these specific functional properties of channels have become well understood through decades of basic electrophysiologic study using the tools of voltage clamp and patch clamp techniques, and more recently, molecular, genetic, and structural/crystallographic techniques.

The structural makeup of most ion channels contains several common motifs. All channels form a central conducting pore, with ionic selectivity determined by specific amino acids that line the central pore. The central pore of most channels is formed by the P domain, a series of hydrophilic amino acid residues, with one of several structural variants: four separate homologous alpha subunits, each with homologous P domains (voltage-gated K channels); a single alpha subunit with four internally homologous P domains (voltage-gated Na or Ca channels); or two internally homologous P domains from two separate subunits (most ligand-gated K channels). A series of one or

more transmembrane segments surrounds the central pore. In voltage-gated channels, the fourth of six segments, the S4 segment, contains a series of charged amino acid residues that functions as a voltage sensor, responding to changes in membrane potential by facilitating protein conformational changes that result in channel opening or closing (gating). In ligand-activated channels, the binding of a ligand (transmitters, molecules, or other ions) results in channel opening or closing, while deformations in membrane shape determine gating in stretch-activated channels. In addition, in many ion channels, a complex of auxiliary proteins is associated with the primary alpha subunit; most auxiliary subunits appear to facilitate regulation of ion channel expression and activity. A distinct type of transmembrane protein complex is the gap junction complex. A large multimeric complex of connexin subunits forms a large, nonselective pore that spans and thereby connects adjacent myocytes. This allows free flux of ions between adjacent myocytes, facilitating impulse propagation across myocardial tissues.

Due to the physiologic gradient of their respective ions across the cell membrane, Na and Ca channels account for most inward, or depolarizing, currents in cardiac myocytes, and these channels respond to membrane depolarization with rapid opening, relatively rapid closing, and inactivation. Na and Ca currents therefore drive phase 0 depolarization of the AP. Potassium channels, on the other hand, account for most of the repolarizing currents seen in cardiac myocytes. Relatively slow K channel opening, as well as Na and Ca channel closing and inactivation, drives the plateau of phases 1–2 as well as the repolarizing phase 3 of the AP. Mutations in K channel subtypes are causative of many inherited channelopathies. Mutations that either inherently delay the closing or inactivation of K channels result in prolongation of the QT interval, leading to many forms of inherited long QT syndrome.

The morphologic and functional properties of APs vary across different regions of the heart. These variations are the result of variations in the active ionic currents during each phase of the AP, which in turn reflects regional variation in ion channel expression. In atrial and ventricular myocytes, Na currents dominate the rapid upstroke

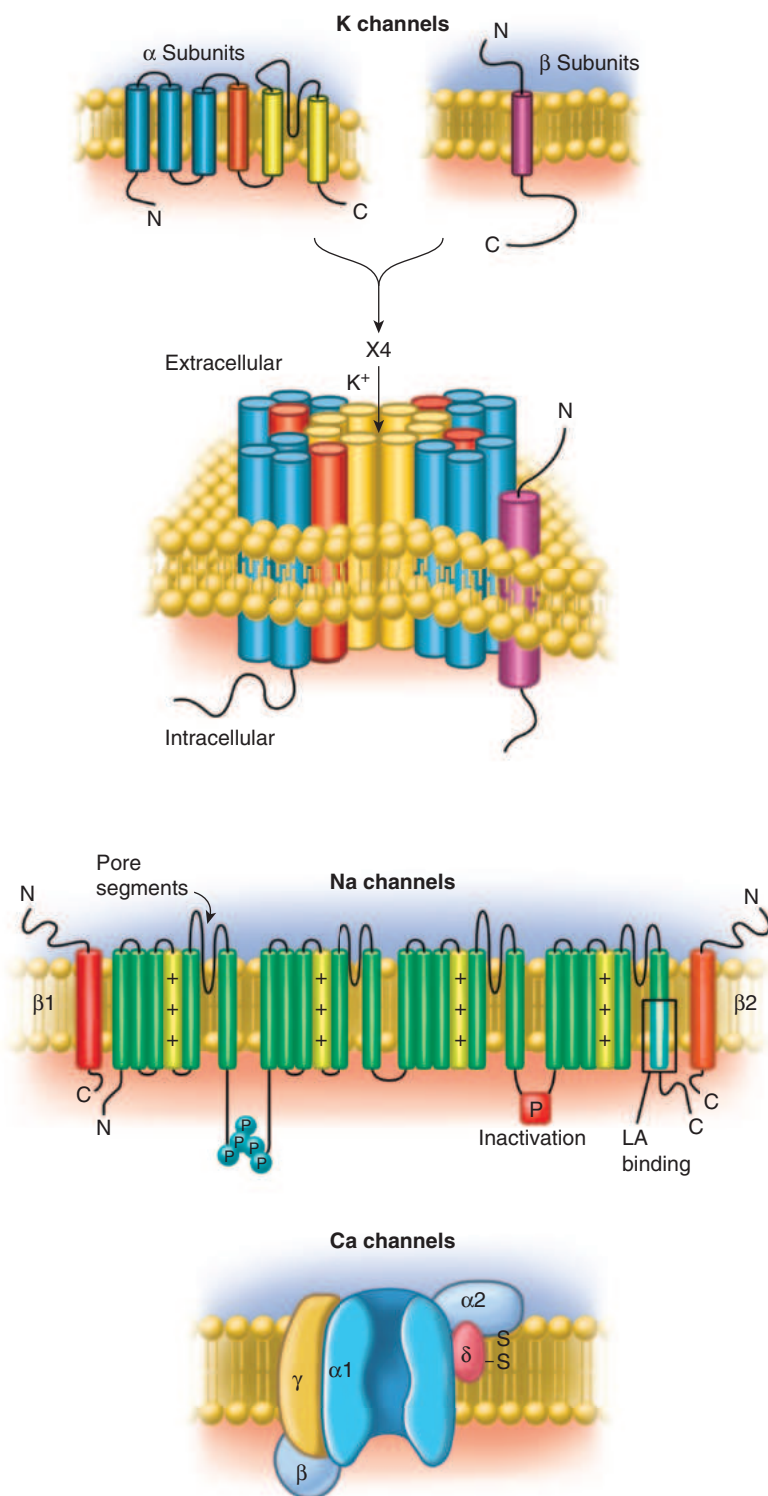


FIGURE 250-2 Topology and subunit composition of the voltage-dependent ion channels. Potassium channels are formed by the tetramerization of α or pore-forming subunits and one or more β subunits; only single β subunits are shown for clarity. Sodium and calcium channels are composed of α subunits with four homologous domains and one or more ancillary subunits. In all channel types, the loop of protein between the fifth and sixth membrane-spanning repeat in each subunit or domain forms the ion-selective pore. In the case of the sodium channel, the channel is a target for phosphorylation, the linker between the third and fourth homologous domain is critical to inactivation, and the sixth membrane-spanning repeat in the fourth domain is important in local anesthetic antiarrhythmic drug binding. The Ca channel is a multi-subunit protein complex with the α_1 subunit containing the pore and major drug-binding domain.

(phase 1) of the AP, while in nodal tissues, Ca currents, which activate more slowly, dominate phase 1. Hence, for instance, drugs that bind and block the cardiac Na channel demonstrate efficacy in treating tachyarrhythmias arising from the atria and ventricles, whereas Ca channel blocking agents demonstrate efficacy at nodal tissues. During

the pre-depolarizing phase 4 of the AP, ionic currents remain relatively quiescent in atrial and ventricular myocytes as they await local depolarization that triggers the next AP. In contrast, in sinus nodal tissues, which possess the property of automaticity, or intrinsic rhythmic depolarization, there is gradual depolarization observed during phase 4, until a threshold is reached that initiates the next AP. In these nodal tissues, this depolarizing phase 4 current is generated by a semiselective Na/Ca channel, termed the “funny current” or I_f , which is the target for the medication ivabradine.

NORMAL CARDIAC IMPULSE PROPAGATION

The normal cardiac impulse initiates and travels through specialized conduction fibers, often referred to as the cardiac conduction system. Each impulse is initiated in the sinoatrial (SA) node, located at the lateral junction between the superior vena cava (SVC) and right atrium (RA). SA nodal tissues exhibit automaticity, such that a reliable, rhythmic impulse emanates from the SA node. The SA node (along with the AV node) is richly innervated by autonomic fibers, allowing precise and dynamic control of heart rate and overall function by the central nervous system. The normal impulse then travels across the RA then the LA across preferential conduction pathways, initiating atrial systole. Once the impulse reaches the AV node, conduction occurs in a relatively slow time frame through the AV nodal tissues. This conduction time not only serves to provide physiologic AV synchrony but also is reflected in the surface ECG as the PR interval, or time between the atrial inscription and the subsequent ventricular, or QRS, complex. In normal hearts, the AV node serves as the only electrical connection between atria and ventricles. Both the SA and AV nodes respond exquisitely to autonomic input; for instance, with exercise and increased adrenergic tone, the PR interval physiologically shortens. After the AV node, the impulse travels through a network of specialized conduction fibers: the bundle of His divides into a right and left bundle branch, which transmit conduction to the right and left ventricles, respectively. The left bundle then divides further into the left anterior and posterior fascicles. The fascicles then further divide into a network of Purkinje fibers. The conduction velocity of electrical impulses is much higher in Purkinje fibers (2–3 m/s) than in myocardial cells (0.3–0.4 m/s). Different connexins in gap junctions of Purkinje networks are partially responsible for more rapid conduction. This network of conductive Purkinje fibers is located endocardially and serves to rapidly transmit depolarization throughout the ventricles, such that myocardial depolarization, and hence mechanical contraction, occur rapidly and in a coordinated, synchronized fashion, optimizing mechanical contraction of the ventricles. Repolarization of the ventricular myocardium, on the other hand, occurs relatively slowly and progresses from the epicardial surface back toward the endocardium. Hence, the T wave inscription in most ECG leads is concordant with the QRS complex.

MECHANISMS OF CARDIAC ARRHYTHMIAS

Cardiac arrhythmias are the manifestation of abnormalities in the initiation and/or propagation of the cardiac electrical impulse. Bradyarrhythmias result most commonly from abnormalities in the specialized conduction tissues. Abnormal function of the SA node may result in pathologic sinus bradycardia; AV node disease may result in conduction block; pathology in the His-Purkinje system may result in conduction block as well. Tachyarrhythmias may arise from not only

TABLE 250-1 Overview of the Mechanisms of Cardiac Tachyarrhythmias

TACHYARRHYTHMIA CATEGORY	MECHANISM	PROTOTYPICAL ARRHYTHMIAS
Abnormal automaticity	Enhanced (acceleration of phase 4 repolarization)	Idiopathic VT; AT
	Suppressed (absent or decelerated phase 4 repolarization)	Sinus node dysfunction
Triggered activity	EADs	TdP in long QT syndrome, PVCs
	DADs	Reperfusion PVCs/VT, AT and VT with digitalis toxicity
Reentry	(1) Anatomic or functional confinement of a circuit (i.e., scar, accessory pathway); (2) unidirectional block after a premature impulse; (3) wave of excitation that travels in a single direction returning to its point of origin	AVNRT, AVRT, atrial flutter, scar-related VT

Abbreviations: AT, atrial tachycardia; AVRT, atrioventricular reentry tachycardia; AVNRT, atrioventricular nodal reentry tachycardia; DADs, delayed afterdepolarizations; EADs, early afterdepolarizations; PVC, premature ventricular contraction; TdP, torsades des pointes; VT, ventricular tachycardia.

nearly every location within the conduction tissues, but also within atrial or ventricular tissues. Tachyarrhythmias are typically classified by mechanism: enhanced automaticity refers to abnormal spontaneous depolarization, which can occur along the conduction system, the atria, or ventricles; triggered arrhythmias result from abnormal afterdepolarizations that occur in either phase 2/3 (early afterdepolarizations) or phase 4 (delayed afterdepolarizations) of the AP; reentry results from circus movement of an electrical impulse (see Table 250-1 and Fig. 250-3).

■ ENHANCED AUTOMATICITY

Automaticity, defined as spontaneous depolarizations occurring during phase 4 of the AP, is a normal property of several myocardial tissues, including the SA node, AV node, and the His-Purkinje system. The automaticity of the SA node triggers the normal cardiac impulse. When the automaticity of a more proximal conduction system tissue

is unreliable or slow, the automaticity of a more distal aspect of the conduction system may result in an “escape rhythm” that may maintain cardiac output. Automaticity in these tissues results from phase 4 depolarization of cellular membranes driven by several ionic currents. In the SA node, the nonselective Na/Ca I_f current drives this depolarization, while in other tissues, K currents, Ca currents, or even the Na/Ca and ATP-driven Na/K exchangers contribute.

The rate of depolarization during phase 4 drives the frequency of APs and hence automaticity rate of these tissues. In nodal tissues, this rate of depolarization is highly regulated by the autonomic system. Parasympathetic input results in local acetylcholine (ACh) release, which then binds the IKACH potassium channel complex (specifically via a G protein-mediated mechanism). The opening of IKACH channels, resulting in K efflux, hyperpolarizes these cells, resulting in slowing of phase 4 depolarization, thereby slowing the automaticity rate. Sympathetic input, via catecholamines, activates both α - and β -adrenergic receptors. β -1 adrenergic stimulation results in activation of L-type Ca channels, Ca influx, and as a result, enhanced depolarization rates during phase 4, and increased automaticity rates. The normal range of SA automaticity rates is between 30 and 220 beats/min, corresponding to the normal range of rates during sinus rhythm. The sinus rate at any instant is therefore a dynamic balance between sympathetic and parasympathetic input, with the latter dominating in the restful state. The intrinsic heart rate (IHR) is defined as the “native” automaticity rate of the SA node, absent any autonomic input.

Abnormally enhanced automaticity may occur at any site that exhibits automaticity, including the SA node, AV node, or His-Purkinje system, resulting in pathologic tachycardia. In addition, in pathologic states, other stereotyped regions in the heart may exhibit enhanced automaticity, including the pulmonary veins, coronary sinus superior vena cava, and ventricular outflow tracts. Injury to myocardium, whether through ischemia or other mechanisms, may alter its cellular membrane properties, resulting in automaticity in these tissues. For instance, the border zones of infarcted ventricular myocardium, or rapidly reperfused ischemic myocardium, often exhibit automatic arrhythmias including premature ventricular contractions (PVCs) or automatic idioventricular rhythms (AIVR). Abnormal automaticity in the pulmonary veins is believed to underpin the triggers that drive paroxysmal atrial fibrillation, while automaticity elsewhere in the atria drives atrial tachycardias.

■ AFTERDEPOLARIZATIONS AND TRIGGERED ARRHYTHMIAS

Afterdepolarizations and triggered arrhythmias refer to abnormal depolarizations that occur in the late phases of the AP (afterdepolarizations) that can initiate sustained arrhythmias. Early afterdepolarizations (EADs) occur typically during phases 2–3 of the AP and may be facilitated by intracellular Ca loading. When the QT interval prolongs, typically in a heterogeneous fashion across the ventricles, EADs may trigger wavefronts of abnormal depolarizations, resulting in torsades des pointes (TdP), a nonsustained or sustained ventricular arrhythmia that may result in cardiac arrest. Medications that prolong QT interval, as well as other QT-prolonging factors including hypokalemia, hypomagnesemia, and bradycardia, predispose the ventricles to EADs, leading to TdP. Electrical remodeling in cardiomyopathies may also predispose to QT prolongation and risk of EADs and TdP.

Delayed afterdepolarizations (DADs) are abnormal depolarizations occurring in phase 4 of the AP. The mechanism underlying DADs is increased intracellular Ca, which then enhances repetitive depolarizations during the late phases of the AP. As a result, repetitive depolarizations ensue, including the well-described phenomenon of bidirectional ventricular tachycardia (VT). Digitalis glycoside toxicity, ischemia, and catecholamines are the most commonly described causes for DADs.

■ REENTRY

Reentry refers to the circus movement of a wavefront of electrical activation. Reentry can occur around a fixed anatomic barrier, referred to as anatomic reentry, or around a functionally blocked or

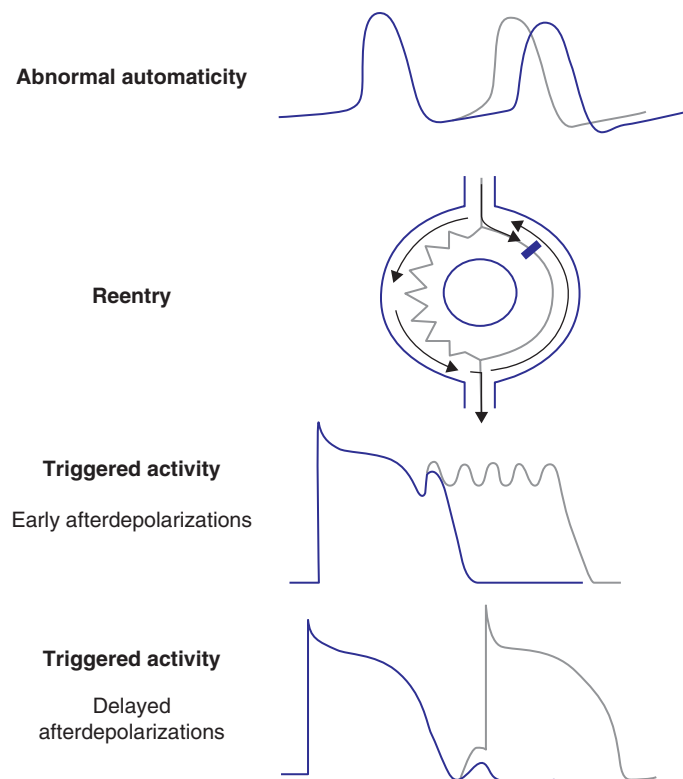


FIGURE 250-3 Schematic action potentials with early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs).

refractory barrier or anchor, termed functional reentry. Initiation and maintenance of a reentrant arrhythmia require (1) unidirectional block, where the electrical wavefront can only propagate in one direction, and (2) slow conduction, a zone within the reentrant circuit where conduction is relatively slow, allowing the remainder of the circuit to repolarize and recover from refractoriness (the inability to reexcite).

The more common form of reentry is anatomic, which requires a defined electrical/anatomic circuit with a pathway around a fixed barrier. A wavefront of depolarization encounters a barrier to conduction that allows propagation in only one direction (unidirectional block), forcing activation preferentially along one limb or pathway. Due to slow conduction, the depolarization wavefront travels through the remaining circuit and continually encounters tissues that have recovered from refractoriness and are hence excitable. This results in perpetual circus movement. Moreover, if the total length of the circuit exceeds a distance determined by the product of the conduction velocity (θ) of the tissue and the refractory period (duration) of that tissue (tr), referred to as the wavelength of tachycardia ($\lambda = \theta \times tr$), an excitable gap, where tissue is recovered from refractory and able to depolarize, is created, allowing reentry. Reentry is the mechanism for several clinically important and common cardiac arrhythmias, including atrial flutter, AV nodal reentry, AV reciprocating tachycardia utilizing an accessory pathway, and scar-based reentrant VT.

When reentry occurs in the absence of a fixed anatomic barrier, it is termed *functional reentry*. A nidus of partially refractory tissue anchors the depolarization wavefront, resulting in a circular or rotational reentrant wavefront. In this case, the reentrant circuit or activity tends to be less stable than that from anatomic reentry, resulting in variations in depolarization rate and propensity to easily terminate and/or reinitiate. There is evidence that functional reentry is the underlying mechanism for perpetuation and maintenance of both atrial fibrillation (AF) and ventricular fibrillation (VF). In both of these apparently chaotic and disorganized arrhythmias, multiple wavefronts resulting from multiple functional reentrant circuits appear to drive arrhythmia in many, if not most, instances. Underlying pathology of the myocardium resulting in heterogeneous electrophysiologic properties, altered activation, and repolarization properties predispose myocardial tissues to initiation and propagation of functional reentry-based arrhythmias.

In addition to intrinsic alterations in cellular membrane electrophysiologic properties that underpin most arrhythmias, extrinsic factors may precipitate other architectural and tissue changes that contribute to proarrhythmia. Ischemia and infarct may create regions of heterogeneous fibrosis, resulting in islands of scar surrounded by injured tissue. This creates the anatomic substrate that can sustain anatomic reentry, which underlies scar-based VT, as well as many macro-reentrant atrial arrhythmias. Peri-infarct border zones often contain injured myocardium as well, and the resultant alterations in cellular membrane properties may promote enhanced automaticity or triggered arrhythmias. Chronic ischemia also results in downregulation of connexin proteins and gap junctions, resulting in slowed impulse propagation, which is one of the factors required for reentrant arrhythmias. Alterations in ion channel function, either through inherited mutations or through drug effect, can promote arrhythmias. QT prolongation can occur when the closing of potassium channels that should hyperpolarize cells is delayed or slowed, or when the closing or inactivation of Na channels is impaired.

■ UNDERPINNINGS OF THE TREATMENT OF ARRHYTHMIAS

Pharmacologic therapies for arrhythmias are directed toward the specific underlying mechanism. For enhanced automaticity-based arrhythmia, medications that target phase 4 depolarization, including Ca channel blockers, beta-adrenergic blockers (via indirect action on adrenergic input), or ivabradine may be used. For triggered activity-based arrhythmia, correcting the precipitating factor is most effective. This includes, among other therapies, removal of digitalis glycosides

from the body, discontinuation of QT-prolonging medications, or even increasing heart rate, thereby shortening QT interval. For reentrant arrhythmia, medications that increase the refractory period, in particular K channel blocking agents, will increase the wavelength of conduction beyond the circuit length of tachycardia, resulting in the inability to sustain reentry. Medications that slow conduction velocity may have the paradoxical effect of promoting reentrant arrhythmias due to the creation of a larger excitable gap. This explains much of the proarrhythmic effect of many antiarrhythmic medications. Therefore, for these agents, which typically include Na channel blockers, sufficient dosing is required to slow conduction velocity to the point of extinguishing meaningful arrhythmia circuit conduction.

A major aspect of clinical cardiac electrophysiology that has evolved over several decades is the ability to disrupt arrhythmic substrates through catheter-based (or rarely surgical) myocardial ablation. For automaticity-based arrhythmias, precise localization and elimination or isolation through ablation of the site of focal automaticity is effective in eliminating arrhythmia. For anatomically bound reentrant arrhythmias, interruption of the reentrant circuit with a series of ablation lesions is effective. In contrast, given the lack of a fixed anatomic circuit, and perhaps also due to the presence of multiple, often migratory, circuits, it appears that mechanical disruption, typically through catheter-based ablation, of identified sites of functional reentry appears to be ineffective in eliminating arrhythmia.

CARE OF THE ARRHYTHMIA PATIENT

■ EVALUATION AND DIAGNOSIS

The evaluation of a patient with suspected arrhythmia begins with a directed history and physical examination, which must include an ECG. The history and examination should focus on determining the nature of symptoms attributable to the arrhythmia itself and clues to potential underlying cardiac, medical, or metabolic conditions that may predispose to specific arrhythmias, and hence direct further studies and evaluations, ultimately directing appropriate therapy, prognosis, and counseling. Family history may also provide clues toward possible inherited arrhythmia syndromes. Symptoms attributable to arrhythmia can vary from a vague sensation of fatigue, chest pain, dyspnea, or lightheadedness to more specific sensations of rapid, slow, or irregular heart rate. Premature contractions, whether atrial or ventricular, may be sensed as extra beats, or if these extrasystoles result in diminished stroke volume for that particular beat, a sensation of a missed beat. Second, the hemodynamic sequelae of impaired cardiac output may result in symptoms, from presyncope to frank syncope, dyspnea, chest discomfort, or generalized weakness. Importantly, as the cadence and duration of arrhythmia episodes are highly variable, the temporal manifestations of arrhythmia symptoms may vary significantly. Sporadic episodes of arrhythmia will result in intermittent symptoms, including syncope if hemodynamic compromise is significant; protracted episodes of arrhythmia may cause persistent symptoms. In patients with underlying compromise in cardiac function, most typically in patients with structural heart disease, arrhythmia leading to diminished cardiac output may trigger or exacerbate symptoms associated with the underlying condition such as angina, congestive heart failure, or hypoxia-associated symptoms.

Inciting factors or associations may also provide clues to the diagnosis. Arrhythmias associated with activities that increase adrenergic tone, such as exercise, stimulant intake, or emotional stress, may suggest not only tachyarrhythmias but also automaticity-triggered arrhythmias. However, keep in mind that exceptions will occur. Medication use may be highly suggestive of an etiology: use of Ca channel blockers or beta blockers may suggest bradycardia exacerbated by these medications. Medications known to potentially prolong QT interval may suggest a malignant ventricular arrhythmia, specifically TdP. Eliciting a thorough family history, not only for known arrhythmia diagnoses, but of unexplained sudden death, may point toward a heritable syndrome. Demographic factors may point toward or away from certain diagnoses. For instance, AF rarely occurs in children and young

adults, save rare familial forms, or AF associated with structural heart disease; a strong male predominance, as well as a higher prevalence in certain ethnic populations such as Southeast Asians, is seen in Brugada syndrome; inappropriate sinus tachycardia is nearly exclusively a condition affecting young women; degenerative conduction system disease leading to symptomatic bradycardia is most commonly a condition seen in older patients.

Arrhythmias may run the gamut from benign to malignant, life-threatening etiologies. Therefore, an important aspect of the evaluation of suspected arrhythmia is to discern patient prognosis, which then informs treatment. Arrhythmias that result in more significant hemodynamic compromise, and therefore more profound symptoms, tend to correlate with more malignant disease. In turn, the higher the suspicion for a malignant arrhythmia, the more aggressive the evaluation will likely be. Loss of consciousness, which may be the result of cardiac arrhythmia but also other etiologies that may be more benign, presents a particularly challenging yet common diagnostic dilemma. Therefore, careful thought into the appropriate evaluation for a patient with syncope is critical. In general, the presence of underlying structural abnormality of ventricular myocardium favors more malignant arrhythmias, both due to the increased risk of lethal ventricular arrhythmias and to potential inability to hemodynamically tolerate any particular arrhythmia. A careful history of circumstances, symptoms, and associated findings during the syncopal episode(s) can be very helpful in formulating a differential diagnosis.

The ECG is the cornerstone and most important diagnostic test that should be performed on every patient with suspected arrhythmia. A 12-lead resting ECG may offer clues to the diagnosis. Most simply, if active arrhythmia is captured on the ECG, a definitive diagnosis can be made. In addition, evidence suggesting underlying cardiac disease, such as prior myocardial infarction, left ventricular hypertrophy and possible hypertrophic cardiomyopathy, atrial disease, or baseline conduction system disease, may suggest a diagnosis. A subset of conditions that predispose to arrhythmia, both inherited or acquired, may be discerned as well, including ventricular preexcitation, prolonged or shortened QT interval, or ECG findings suggestive of specific inherited conditions such as Brugada syndrome or right ventricular cardiomyopathy.

However, the ECG typically records only 6 s of cardiac electrical activity, and therefore more intermittent and transient arrhythmias, particularly those not typically associated with abnormalities on the resting ECG, may not be seen. Many arrhythmias, including forms of both supraventricular tachycardia (SVT) and VT, can only be diagnosed definitively if an ECG is performed during active arrhythmia and/or symptoms from arrhythmia or, alternatively, provoked in the electrophysiology laboratory. Therefore, various forms of ambulatory monitoring may be performed to attempt to capture ECG activity during active arrhythmia. A growing variety of monitoring options are available; the most appropriate option should be primarily guided by the cadence of suspected arrhythmia episodes. For instance, if daily symptoms occur, a 24- or 48-h continuous Holter monitor is appropriate. On the other hand, a patient-activated event recorder is inappropriate in a patient with syncope, as the arrhythmic event will likely have passed once the patient reawakens.

Attempts at provoking arrhythmia may be warranted in the appropriate circumstances. An ECG-monitored treadmill test may elicit exercise-induced arrhythmias, or if long QT is suspected, a QT interval that fails to shorten appropriately with increased heart rate may be helpful. Pharmacologic provocation may be indicated for certain suspected diagnoses, such as Brugada syndrome. Judicious and appropriate use of carotid sinus massage or other means to enhance vagal tone may be helpful to diagnose carotid hypersensitivity or overall vagally mediated syncope.

Tilt table testing (TTT) involves having a patient strapped to a tiltable table. While monitoring heart rate and blood pressure, the patient is moved from a supine to upright position. In patients with suspected autonomic dysfunction-mediated syncope or presyncope, this provocation may elicit a paradoxical vagal response, resulting in bradycardia and/or sinus pauses as well as hypotension, and perhaps

frank syncope. However, given the significant lack of both sensitivity and specificity, the current role of TTT is unclear, and it is seldom indicated after a careful history elucidates a neurally mediated cause for syncope.

Invasive electrophysiologic (EP) testing is the most useful diagnostic modality for many arrhythmias. Catheter-based recordings of intracardiac electrograms, with or without provocative pacing or pharmacologic maneuvers, may elicit the clinical arrhythmia. This will, in turn, help to define the mechanism of arrhythmia. However, one must keep in mind that for certain arrhythmia mechanisms, such as automaticity-driven tachycardia, EP study may fail to elicit arrhythmia due to the often transient and multifactorial nature of initiation of these arrhythmias. The nature of arrhythmia elicited will aid in determination of the patient's prognosis. In a typical EP study, catheters are placed within the heart via femoral venous access. Baseline conduction properties are measured. Provocative maneuvers including electrical pacing maneuvers, programmed stimulation, and pharmacologic provocation are performed. In the modern era, the vast majority of invasive EP studies are performed in conjunction with planned catheter ablation, although programmed ventricular stimulation for risk stratification of sudden death may still be utilized. EP study during catheter ablation is performed to confirm the diagnosis, localize appropriate ablation targets, and evaluate the efficacy of ablation performed during the procedure.

Depending on the suspected arrhythmia diagnosis, further testing may be indicated. If structural heart disease is suspected, echocardiography is most often the best next test, as it can assess for underlying structural disease, evaluate left ventricular function, and assess atrial dimensions and mitral valve function if AF is suspected, both of which are fair prognostic indicators. In patients in whom underlying coronary artery disease is suspected, an evaluation for coronary ischemia is indicated. Further evaluation for underlying structural heart disease will be directed based on the differential diagnosis. Cardiac computed tomography provides broad diagnostic utility, depending on the scanning protocol, including evaluation for ischemia, ventricular scar, anatomic evidence of coronary artery disease, congenital anomalies, and left atrial anatomy. Cardiac magnetic resonance imaging provides significant resolution of soft-tissue characteristics and may be used to assess for ischemia, infarct, cardiomyopathy, or infiltrative disease. Cardiac positron emission tomography can also discern underlying ischemia, as well as metabolic/inflammatory/infiltrative conditions.

TREATMENT

Cardiac Arrhythmias

ANTIARRHYTHMIC DRUG THERAPY

The effects of pharmacologic agents on cardiac electrophysiologic properties are often complex and, in some instances, remain incompletely understood. The complexity is the result of complex pharmacodynamics and pharmacokinetics, in particular significant cross-reactivity of certain drugs across different targets as well as variable effects on drug targets across drugs within the same category. There are regional differences in drug effect within the myocardium, and interpatient variations in drug metabolism play important roles. This has, in part, led to many instances of harm that have come from the adverse effects of many agents used over the years. In fact, many antiarrhythmic agents currently in use carry significant risks of side effects, some of which may be significant and even lethal. Therefore, judicious use of antiarrhythmic medications by those with appropriate knowledge base and experience is warranted. The practical result of the narrow therapeutic index of this class of medications has rendered their use increasingly as ancillary options ([Table 250-2](#)).

The traditional nomenclature of antiarrhythmic drugs (AADs) is known as the Vaughan-Williams classification schema. In this schema, there are four classes (I–IV; [Table 250-2](#)). Class I AADs primarily target the Na channel, class II agents target the

TABLE 250-2 Antiarrhythmic Drug Actions

DRUG	CLASS ACTIONS				OTHER ACTIONS/COMMON SIDE EFFECTS
	I	II	III	IV	
Quinidine	++		++		Anticholinergic
Flecainide	+++		+		Can promote reentrant arrhythmias (atrial flutter, ventricular tachycardia)
Propafenone	++	+			Mild beta-blocker effect
Amiodarone	++	++	+++	+	Multiorgan toxicity with long-term use
Sotalol		++	+++		Prominent beta-blocker effect
Dofetilide			+++		Prolongation of QT at slower heart rates
Dronedarone	+	+	+	+	Mild effect
Ibutilide			+++		Used only for acute cardioversion
Ranolazine	++		++		Late sodium channel blockade
Lidocaine	++				Used for reperfusion arrhythmias

beta-adrenergic receptor, class III agents target potassium channels, and class IV agents target Ca channels. Class I agents are further subdivided into three subclasses based on the kinetics of drug to Na channel interactions. Class IA agents, including procainamide and quinidine, possess intermediate binding kinetics and potency. Class IB agents, including lidocaine and mexiletine, possess rapid binding kinetics and relatively low potency. Class IC agents (flecainide, propafenone) possess slow kinetics and high potency. Class II agents consist entirely of beta-adrenergic blocking agents. Class III agents (sotalol, dofetilide, ibutilide) specifically target the Kv11.1 potassium channel (encoded by the *KCNH2* gene) and risk prolongation of the QT interval through these effects on phases 2/3 of the AP and hence ventricular repolarization. Class IV agents are cardioselective Ca channel blockers including verapamil and diltiazem. This classification has significant limitations, however. Many AADs interact with multiple ion channels, and as a result, many exhibit behavior consistent with multiple classes. Amiodarone, in particular, exhibits properties of all AAD classes. Adenosine, with primary antiarrhythmic effects as an acute and transient, intravenously administered AV nodal blocking agent, as well as digitalis glycoside, which blocks the Na⁺/K⁺ pump, which in turn inhibits the Na⁺/Ca⁺⁺ exchanger, resulting in antiarrhythmic effect, do not neatly fit into this classification schema.

CATHETER ABLATION

The rationale that underlies catheter ablation for cardiac arrhythmia is that an anatomic substrate can be identified and localized, and disruption or isolation of that substrate will eliminate the cardiac arrhythmia. For automaticity-driven arrhythmias, a focal source of automaticity is identified, localized, and ablated. For anatomic reentrant arrhythmias, a critical zone of slow conduction that sustains arrhythmia and can be reasonably targeted is ablated. Moreover, the ablation target must be in a location deemed at acceptable risk of not damaging critical structures such as the native conduction system, coronary arteries, or extracardiac structures including the esophagus and phrenic nerve. Advances in electroanatomic mapping, a technology that uses alterations in electrical impedance and a magnetic field as measured by an intracardiac mapping catheter, have allowed for real-time reconstruction of cardiac chambers and identification of arrhythmogenic tissue to be targeted for ablation while safely avoiding nontargeted critical structures. Intracardiac echocardiography has also been used to enhance the safety and efficacy of invasive electrophysiologic procedures with real-time visualization of cardiac structures (Fig. 250-4).

In the 1950s–1960s, as the underlying anatomic substrates for arrhythmias became better understood, open surgical disruption of arrhythmia circuits was the only available interventional and curative therapy for many arrhythmias. Surgical ligation of accessory pathways or resection of ischemic VT substrates was performed at specialized surgical centers. The first attempts at clinical catheter ablation utilized direct current (DC) electrical energy. This resulted in a high-voltage pulse of electrical energy that would ablate cardiac tissue, but with a difficult-to-control scope, often leading to significant complications. Radiofrequency (RF) energy was adapted to catheter-based cardiac ablation in the 1980s. RF alternating electrical current (300–550 kHz) delivered through a catheter tip results in local tissue heating and permanent injury, rendering the targeted tissue electrically inert. This type of ablation is similar to the technology used in electrosurgical techniques using a Bovie electrocautery device. For >35 years, RF delivery via catheters has been iteratively optimized such that it has become the most common and mainstay energy source for catheter ablation. Catheter ablation is indicated for a wide variety of clinical arrhythmias, including SVT, accessory pathways, atrial flutter, AF, PVCs, and VT. Alternative

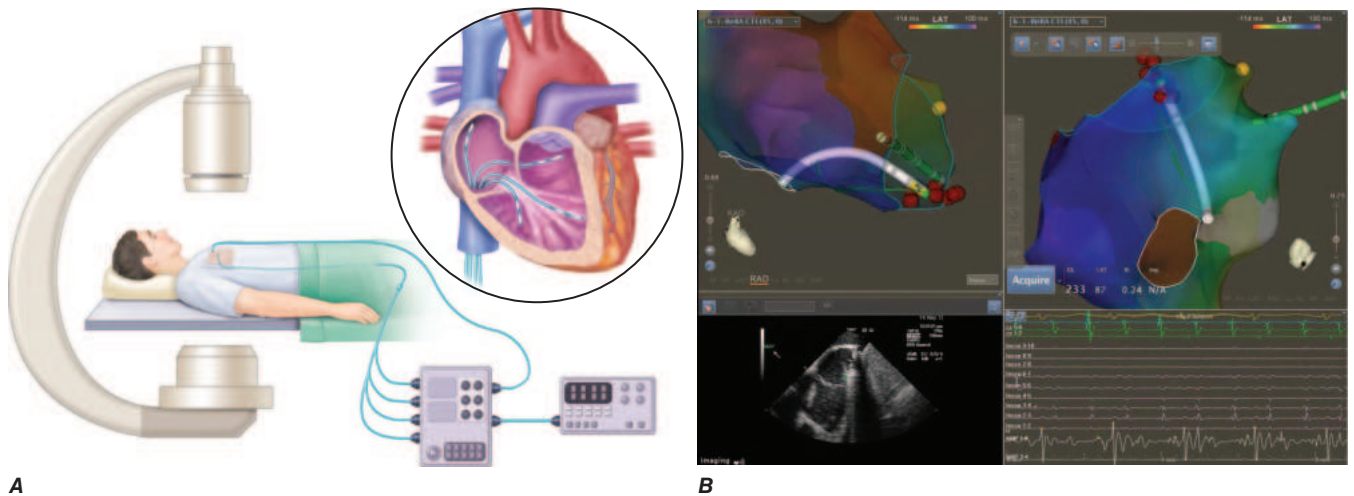


FIGURE 250-4 Catheter ablation of cardiac arrhythmias. A. A schematic of the catheter system and generator in a patient undergoing radiofrequency catheter ablation (RFCA); the circuit involves the catheter in the heart and a dispersive patch placed on the body surface (usually the back). The inset shows a diagram of the heart with a series of intracardiac catheters placed via the inferior vena cava (IVC), typically through femoral venous access. Catheters are located at the high right atrium, His bundle location, right ventricular (RV) apex, and through a transseptal puncture within the left atrium. **B.** Images from an electroanatomic mapping system are shown during mapping and ablation of typical cavo-tricuspid isthmus-dependent atrial flutter. This system allows three-dimensional real-time localization and annotation of catheter position and cardiac anatomy to guide mapping and ablation. In this instance, two projections of the map are shown at the top of the right atrium (RA), a right anterior oblique (RAO) and left anterior oblique (LAO) caudal view. Annotations of ablation lesion delivery are shown as red dots. In the left lower aspect of this panel, a simultaneous image from intracardiac echocardiography (ICE) is shown of the RA, with the ablation catheter in view in all three images. In the lower right aspect of this panel, surface electrocardiogram and intracardiac electrograms acquired in real time are shown.

ablative energy sources have been explored over the years, including cryotherapy, light spectrum (laser), microwave, ultrasound, and more recently pulsed field electroporation, which injures targeted myocardium through high-energy, ultra-short pulses of electrical current that disrupts the lipid cell membrane, resulting in permanent cell death. Recently, the well-established ablative technique of stereotactic (focused and directed) external beam ionizing radiation has been applied to the heart to treat various arrhythmias, including VT and AF. This particular treatment modality holds promise given its ability to target regions of the heart that may be inaccessible to catheters, as well as the completely noninvasive nature of the procedure.

A widely applied non-RF ablative energy source today is cryotherapy, where an ablative catheter tip is cooled to a temperature range (typically below -40°C) that results in permanent tissue death. Cryotherapy is most widely applied to ablation of paroxysmal atrial ablation, via an expandable balloon introduced sequentially into each pulmonary vein and cooled to produce a circumferential ablative lesion at the ostium/antrum of each pulmonary vein. Similar catheter-based tools utilizing pulsed field ablation (PFA) have also been introduced for the purpose of electrically isolating pulmonary veins during AF ablation.

IMPLANTED ELECTRICAL DEVICE THERAPY

Implanted cardiac rhythm management devices are commonly utilized to manage arrhythmia. The first definitive pacemaker was implanted in 1958, and this technology has evolved to be the mainstay in the management of bradyarrhythmias. Sinus node dysfunction and AV conduction disease, particularly with symptoms, are the primary indications for most implanted pacemakers. Pacemakers are typically implanted percutaneously, with insulated wires, or leads, inserted through the upper extremity venous system into the right atrial and/or ventricular myocardium, with the lead tip secured to the myocardium mechanically. The leads are connected to a pulse generator placed in the prepectoral space, which contains electronic circuitry and a battery, allowing sensing and/or delivery of pacing stimuli to maintain adequate heart rate. More recently, a completely leadless pacemaker inserted through a large femoral venous sheath directly into the RA or right ventricle endocardium has become available. Although these devices possess more limited pacing options, they likely reduce the risks associated with transvenous lead systems, including infection or lead fracture requiring extraction.

Implanted cardioverter-defibrillators (ICDs) are placed in a similar fashion to pacemakers. However, ICDs have the ability to sense abnormal ventricular arrhythmias and deliver either anti-tachycardia pacing or defibrillation to prevent sudden death. In patients who experience a potentially lethal ventricular arrhythmia, ICD therapy may be lifesaving. Indications for ICD therapy are considered for either primary prevention of sudden cardiac death (SCD) due to arrhythmia in an at-risk patient or as secondary prevention in a patient who has survived an SCD event. More recently, a completely subcutaneous ICD system has become available, avoiding intravenous leads that increase risk for systemic infection, and potentially the procedure to extract a potentially fibrosed lead in cases of lead malfunction or endovascular infection.

FURTHER READING

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251

The Bradyarrhythmias: Disorders of the Sinoatrial Node

William H. Sauer, Bruce A. Koplan

The sinoatrial (SA) node serves as the natural pacemaker of the heart and has variable rates in response to parasympathetic and sympathetic stimulation. If the sinus node is dysfunctional or suppressed, a subsidiary pacemaker in the atrioventricular node or specialized conduction system will take over, leading to a junctional or ventricular rhythm. Symptoms of sinus node dysfunction can vary but typically present as fatigue, exercise intolerance, or dyspnea. The diagnostic evaluation includes an investigation into reversible causes of sinus bradycardia, confirmation of sinus node dysfunction with outpatient telemetry monitoring or exercise testing, and possibly cardiac imaging if structural heart disease is suspected. Once irreversible sinus node dysfunction is confirmed, permanent pacemaker implantation is the only reliable long-term therapy for symptomatic bradycardia.

STRUCTURE AND PHYSIOLOGY OF THE SA NODE

The SA node region is complex in structure. Clusters of myocytes with pacemaker activity are surrounded by fibroblasts, endothelial cells, and transitional cells. These clusters of small fusiform cells in the sulcus terminalis on the epicardial surface of the heart at the right atrial–superior vena cava junction envelop the SA nodal artery. The SA node is structurally heterogeneous, but the central prototypic nodal cells have fewer distinct myofibrils than does the surrounding atrial myocardium, no intercalated disks visible on light microscopy, a poorly developed sarcoplasmic reticulum, and no T tubules. Cells in the peripheral regions of the SA node are transitional in both structure and function. The SA nodal artery arises from the right coronary artery in 55–60% and the left circumflex artery in 40–45% of persons. This feature, along with a protective extracellular matrix of connective tissue, insulates the SA node from the hyperpolarizing influence of the larger atrium. In addition, the alignment of this complex matrix is associated with nearly unidirectional electrical propagation to the atrium (Fig. 251-1).

Pacemaker cells spontaneously depolarize in a continuous manner setting the natural rate of depolarization and myocardial contraction. Action potential depolarization in the SA node is normally at a resting rate of 60–100 beats/min. The autonomic nervous system exhibits control over the sinus node, with a preponderance of parasympathetic innervation at baseline. Removal of parasympathetic tone or an increase in sympathetic innervation leads to an increase in rate of depolarization. In denervated hearts, the rate of electrical depolarization (intrinsic heart rate) is approximately 100 beats/min, reflecting the rate of automaticity of the sinus node uninhibited by parasympathetic tone. The complement of ionic currents present in nodal cells results in a less negative resting membrane potential compared with atrial or ventricular myocytes. Electrical diastole in nodal cells is characterized by slow diastolic depolarization (phase 4), which generates an action potential as the membrane voltage reaches threshold. The action potential upstrokes (phase 0) are slow compared with atrial or ventricular myocytes, being mediated by calcium rather than sodium current.

Cells with properties of SA nodal tissue are electrically connected to the remainder of the myocardium by cells with an electrophysiologic phenotype between that of nodal cells and that of atrial or ventricular myocytes. Cells in the SA node exhibit the most rapid phase 4 depolarization and thus are the dominant pacemakers in a normal heart.

Myocytes within the SA node complex include specialized cells surrounded by fibrous tissue. Unlike atrial and ventricular cells, sinus node pacemaker cells have no true resting potential, but instead depolarize automatically and repetitively after the end of an action potential, and the depolarizing current in the SA node myocytes results primarily from slow calcium currents instead of fast sodium channels, which are

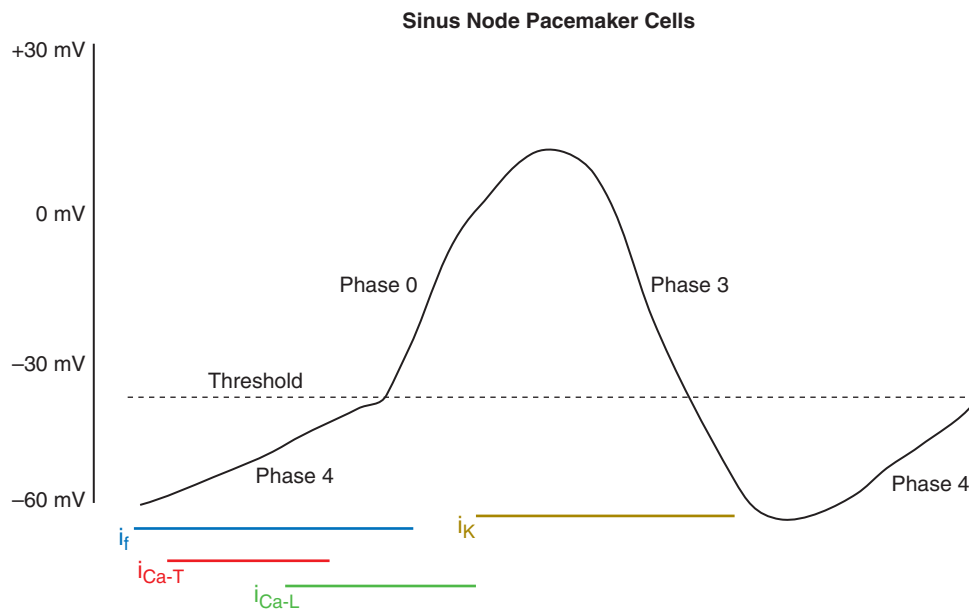


FIGURE 251-1 Cellular ion currents involved in depolarization and automaticity of sinoatrial (SA) nodal pacemaker cells. Phase 4 spontaneous depolarization results from i_f (funny) current, along with T- and L-type calcium channels. Phase 0 is the depolarization phase of the action potential. This is followed by phase 3 repolarization, which results from the outward directed hyperpolarizing K^+ currents. i_f , funny current; i_{Ca-T} , T-type calcium current; i_{Ca-L} , L-type calcium current; i_K , potassium current.

absent in SA node cells. Spontaneous phase 4 depolarization results from a combination of slow inward depolarizing sodium current (I_f , “funny current”), along with inward calcium current controlled by T-type and L-type calcium channels. The upstroke of depolarization in SA node myocytes is slower and lower in amplitude than in ventricular myocytes.

In patients <85 years of age, the resting heart rate is strongly influenced by parasympathetic tone at baseline. The absence or elimination of autonomic influence on the SA node (e.g., after atropine administration) leads to an intrinsic heart rate that is normally 100–110 beats/min. The myocytes within the SA node that initiate pacing will change with different rates with a superior shift at higher heart rates and an inferior shift at lower rates. This shift may lead to a slightly different P wave inscribed on electrocardiograms (ECGs) recorded during different rates of sinus rhythm.

In addition, a progressive decline in maximum heart rate occurs with age, although the resting heart rate normally remains unchanged. Intrinsic heart rate declines 5–6 beats/min for each decade of age. However, the constancy of resting heart rate is associated with a gradual decrease in parasympathetic tone and a transition to predominant sympathetic tone by the ninth decade.

■ DIAGNOSIS OF SA NODAL DISEASE

Intrinsic sinus node disease is sometimes referred to as sick sinus syndrome or sinus node dysfunction (SND) and can manifest as fatigue, exercise intolerance, or syncope resulting from either reduced heart rate or pauses. Electrocardiographic recording plays a central role in the diagnosis and management of SA node dysfunction. The correlation between symptoms and slow heart rate or pauses is essential in determining whether bradycardia may be considered pathologic and necessitating intervention. Baseline ECG can detect baseline sinus bradycardia but may not indicate symptom correlation in certain settings. To address the limitations of the resting ECG, longer-term recording employing mobile telemetry devices such as Holter monitors or mobile cardiac telemetry can also be helpful in correlating symptoms with rate abnormalities (Fig. 251-2).

In addition, commercially available wearable devices, such as watches with ECG recording capabilities, can have electrograms with excellent fidelity that may also be utilized. Contemporary event monitors may be automatically triggered to record the ECG when certain programmed heart rate criteria are met and implantable monitors permit very long-term recording (years) in particularly challenging patients. Treadmill testing can be utilized to assess for maximum heart rate. It is worth noting, however, that standard Bruce protocol treadmill testing may

be helpful in detecting abnormalities in maximum heart rate, but more insidious chronotropic incompetence that manifests as abnormalities of rate increase during submaximal exercise may be more evident with treadmill protocols that have more gradual effort increases.

Once there is evidence of SND, it is important to rule out reversible causes of resting sinus bradycardia or chronotropic incompetence. Table 251-1 lists the potentially reversible causes of sinus node disease and includes hypothyroidism and rate-slowing medications. Many patients with sleep apnea will have high vagal tone during sleep, especially during apneic events. Sinus bradycardia and sinus pauses frequently are seen if a patient is being monitored during this period. Sleep apnea, a common reversible cause, should be suspected if marked sinus bradycardia and prolonged sinus pauses are observed in a telemetry monitoring period during sleep. It is also worth noting that asymptomatic sinus bradycardia and pauses during sleep are typically not an indication for pacing, and it is, therefore, important when interpreting a wearable monitor to determine the timing of bradycardia events with regard to the sleep versus awake periods.

If structural heart disease is suspected, transthoracic echocardiography should be used to detect potential cardiac abnormalities associated with SND (Fig. 251-3). Advanced cardiac imaging is indicated for evaluation of possible myocardial diseases such as amyloidosis, infiltrative cardiomyopathy, or myocarditis. Invasive electrophysiology testing solely to assess sinus node function is rarely utilized beyond the noninvasive techniques mentioned. In patients who are undergoing electrophysiology studies (EPS) for other indications, evaluation of sinus node function as part of the EPS may be considered. In symptomatic patients with suspected SND, EPS may rarely be considered when the diagnosis remains uncertain and after initial noninvasive evaluation is inconclusive. Investigation of the sinus node during EPS can consist of determination of sinus node recovery time (SNRT) and sinoatrial conduction time (SACT). In addition, the intrinsic heart rate [$118.1 - (0.57 \times \text{age})$] can be assessed via pharmacologic blockade of autonomic tone with intravenous propranolol and atropine. EPS is not widely used, however, as there is no evidence that abnormal SNRT or SACT alone can be used as an absolute indication for permanent pacing (PPM). There is no indication for EPS in asymptomatic patients with sinus bradycardia.

■ SA NODAL DYSFUNCTION SUBTYPES

SND can be categorized into problems with impulse formation and problems with impulse conduction. The term *sick sinus syndrome* may be used interchangeably with SND and refers to a group of related

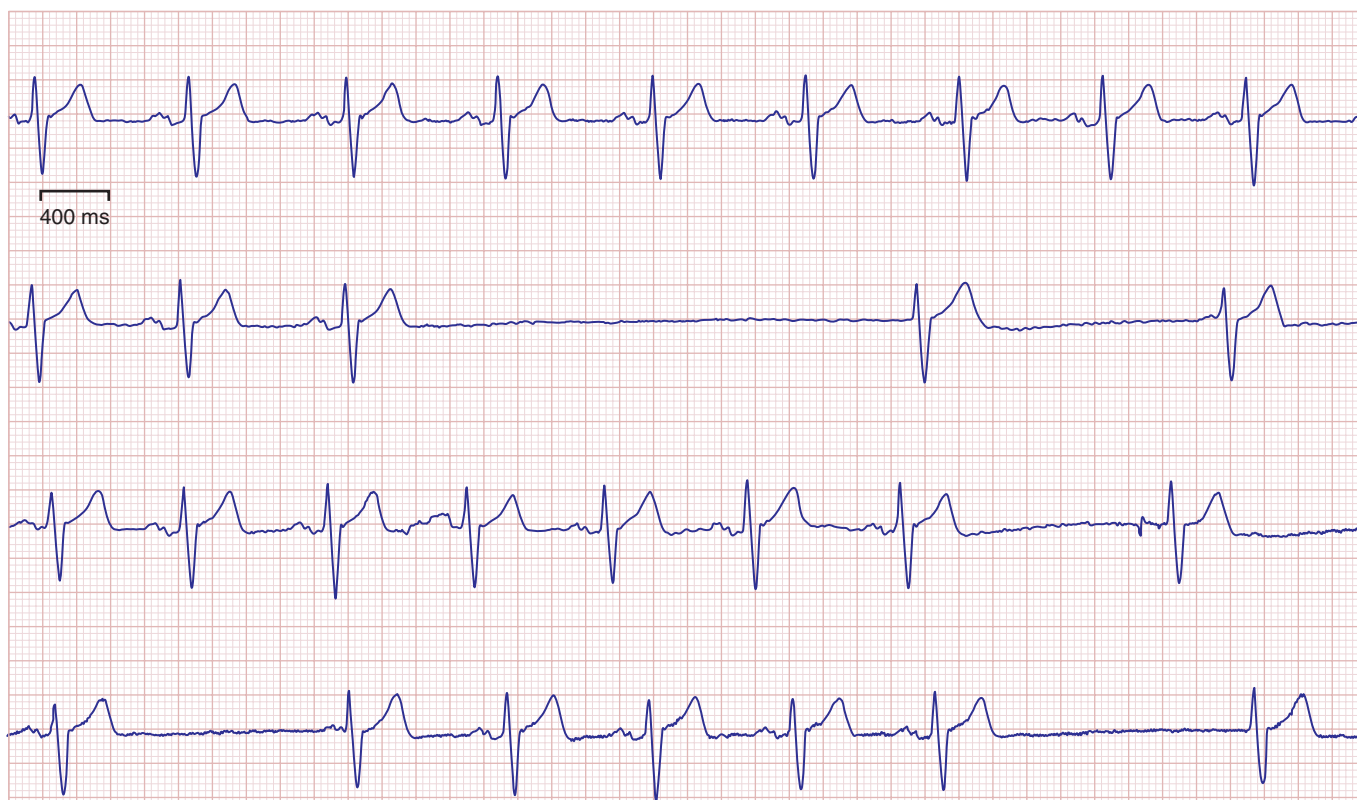


FIGURE 251-2 Sinoatrial exit block. A pause in the heart rhythm is seen that results from a sinus pause. On the second line of the tracing, there is a pause that results from the absence of a sinus beat (absent P wave) and no subsequent QRS. This is followed by a junctional escape beat and eventually recovery of the presence of sinus rhythm P waves.

conditions comprising problems of both impulse formation and impulse conduction.

Sinus Node Exit Block (See Fig. 251-4) “Sinus arrest” results from failure of impulse formation within the sinus node. Sinoatrial exit block results from failure of sinus node activity to propagate to the atrium. Sinoatrial exit block can have similar pattern characteristics of types of atrioventricular (AV) node block. It can manifest as complete SA block. Type I SA block involves fixed delay out of the sinus node. Type II SA block can occur with either progressive delay and then intermittent failure to propagate to the atrium (Mobitz I type) or fixed delay with intermittent failure to conduct (Mobitz II). The mass of the sinus node is not large enough to have an appearance on the ECG. Instead, the P waves that result from atrial depolarization can provide information that reflects the health of the sinus node. Type II second-degree SA block can be inferred on the ECG if the sinus rate abruptly transitions to a sinus rate that is half the previous rate (every other sinus depolarization is blocked from exiting to the atrium). Sinoatrial Wenckebach can be inferred from the ECG in the setting of progressive shortening of the P-P interval leading up to a sinus pause. This is due to progressive prolongation of SA conduction, but to a lesser extent with each successive prolongation. This is similar to the typical progressive shortening of the R-R interval that is observed with AV nodal Wenckebach. Other types of SA block require invasive EPS to decipher. The exercise of determining the type of SA block with invasive electrophysiology testing is typically not necessary because it does not alter management.

Tachy-Brady Syndrome Tachycardia-bradycardia (tachy-brady) syndrome is a subset of sick sinus syndrome/sinus node disease that consists of high heart rates (most commonly atrial fibrillation) with alternating symptomatic bradycardia or offset pauses (Fig. 251-5). Commonly, medications that are needed for rate control of tachycardia exacerbate bradycardia episodes, and thus the presence of tachy-brady syndrome is often a reason to consider pacemaker implantation.

Chronotropic Incompetence Chronotropic incompetence (CI) is broadly defined as the inability of the heart to increase its rate to meet activity or demand. Compared to an increased stroke volume, the increase in heart rate is a stronger contributor to the increase in oxygen uptake (VO_2) during aerobic exercise. Therefore, CI can be the primary cause of severe exercise intolerance and increased cardiovascular events and overall mortality. Unfortunately, CI lacks a consistent definition, leading to a lack of clarity on its overall prevalence. CI can take many forms, including failure to achieve a percentage (e.g., 85%) of age-predicted maximal heart rate $[(220 - \text{age}) \times 0.85]$ during stress testing. Other definitions that have been used include an overall a maximum heart rate $[208 - (0.7 \times \text{age})]$, heart rate instability with exercise, or failure to achieve submaximal heart rate. Due to this latter category, standard exercise testing can, at times, fail to recognize a patient with CI because some patients can achieve an appropriate maximum heart rate but may exhibit heart rate instability or inadequate heart rate during activities of daily living (ADLs). Ambulatory heart rate monitoring along with a diary can be helpful to correlate symptoms with abnormally slow heart rates. Because CI can be insidious and multiple definitions exist, it can be easily overlooked.

Sinus Node Fibrosis Clinical SND is most common in older adults. This is due to normally occurring age-associated increase in fibrotic tissue in the SA node, which can exacerbate any degree of SND. A loss of pacemaker cells in the sinus node is also seen with age. It is worth noting, however, that while increased fibrosis in the SA node and decreased numbers of pacemaker myocytes are part of a normal process of aging, SND is pathologic and there are many elderly patients with extensive fibrosis and normal heart rate.

SA Nodal Ischemia and Infarction Sinus bradycardia is common in patients with acute inferior or posterior myocardial infarction (MI) and can be exacerbated by increased vagal tone (Bezold-Jarisch reflex) or with the use of drugs such as morphine and beta blockers. Ischemia of the SA nodal artery occurs in acute coronary syndromes

TABLE 251-1 Reversible Causes of Sinus Node Dysfunction**Medical Conditions Associated with Sinus Bradycardia**

- Hypothyroidism
- Sleep apnea
- Hypoxia
- Hypothermia
- Increased intracranial pressure
- Lyme disease
- Myocarditis
- COVID-19
- Vagal reflex (cough, pain, etc.)

Medications Associated with Sinus Node Dysfunction**Antihypertensive Medications**

- Beta-adrenergic receptor blockers
- Clonidine
- Methyldopa
- Nondihydropyridine calcium channel blockers

Antiarrhythmic Medications

- Amiodarone
- Dronedarone
- Flecainide
- Procainamide
- Propafenone
- Quinidine
- Sotalol
- Ivabradine

Psychiatric Medications

- Donepezil
- Lithium
- Opioid analgesics
- Phenothiazine antiemetics and antipsychotics
- Phenytoin
- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants

Other

- Anesthetic drugs (propofol)
- Cannabis
- Digoxin
- Muscle relaxants

more typically with involvement with the right coronary artery, and even with infarction, the effect on SA node function most often is transient. However, there are rare cases where SA infarction can affect sinus node function. One potential rare complication of atrial fibrillation catheter ablation is the inadvertent injury to the SA nodal artery that may be coursing over a targeted ablation region in the right and left atrium. SND and arrest have been described following ablation of atrial fibrillation and flutter.

Carotid Sinus Hypersensitivity and Neurally Mediated Bradycardia Sinus bradycardia is a prominent feature of carotid sinus hypersensitivity and neurally mediated bradycardia associated with the cardioinhibitory variant of vasovagal syncope. Carotid hypersensitivity with recurrent syncope or presyncope associated with a predominant cardioinhibitory component responds to pacemaker implantation. Although the vasodepressor effect of the enhanced vagal tone may be unaffected by the pacing support, the lack of bradycardia often prevents injury with this subtype of vasovagal syncope. Several randomized trials have investigated the efficacy of permanent pacing in patients with drug-refractory vasovagal syncope, with mixed results. Although initial trials suggested that patients undergoing pacemaker implantation have fewer recurrences and a longer time to recurrence of symptoms, at least one follow-up study did not confirm these results.

TREATMENT**SA Nodal Disease****TEMPORARY PACING FOR TRANSIENT SUPPORT**

In symptomatic patients presenting with sinus node disease, removing any possible reversible cause remains the initial strategy. Acute myocardial infarction, electrolyte abnormalities, medications, and hypothyroidism should all be considered as potentially reversible causes. Unnecessary medications that may be causing bradycardia should be eliminated. Beta blockers, calcium channel blockers, and digoxin are some of the more common medications in use that may cause bradycardia. These drugs may have a wide range of indications in patients after MI and with chronic systolic dysfunction. If stopping the medication or decreasing the dose is an option, this should be tried first. If the medication is felt to be unavoidable, a pacemaker may be indicated.

In patients with tachy-brady syndrome, alleviation of the tachycardia, whether it is atrial fibrillation or other forms of supraventricular tachyarrhythmias, can prevent bradycardia events. Treatment of the tachycardia can sometimes be accomplished with antiarrhythmic drug therapy or catheter ablation. If arrhythmia control cannot be achieved, permanent pacing may be necessary.

Hypoxia from decrease in blood flow to the SA node, which can occur with cardiac ischemia or MI, can lead to slowing of phase 4 depolarization and resultant bradycardia. Further ischemia and necrosis of pacemaker cells can cause irreversible sinus node disease. On occasion, reversal of ischemia with revascularization can alleviate bradycardia. Sinus pauses in the setting of tachy-brady syndrome may be eliminated if atrial tachyarrhythmias can be successfully treated. It is also important to recognize when bradycardia may be transient. Acute illness associated with episodes of extreme vagal tone may lead to transient SA node abnormalities. Typically, this may be observed as sinus slowing, followed by transient sinus arrest and/or AV block. Although a pacemaker may be needed in extreme instances of prolonged arrest, recovery from the acute illness may make the pacemaker unnecessary in follow-up.

Sinus bradycardia may also be observed after heart transplantation and cardiac surgery. Due to cardiac denervation, a normal resting heart rate in heart transplant recipients is generally 90–110 beats/min. Therefore, a heart rate that may be normal in a non-transplant patient may represent CI in a transplanted patient. In the case of heart transplantation, sinus bradycardia may be due to accumulated drugs such as amiodarone that affect the donor heart or ischemic injury to the SA node upon transplantation. If the SA nodal artery is injured at the time of right atriotomy during cardiac surgery, sinus arrest with junctional rhythm may be observed. Temporary pacing or pharmacologic support with beta-1 adrenergic agonists may be needed in these circumstances while awaiting SA nodal recovery.

In addition, sinus bradycardia and sinus pauses are common after spinal cord injury. The mechanism of bradycardia is enhanced parasympathetic tone and autonomic dysreflexia. Common triggers can be tracheal suctioning and turning the patient. Atropine and inotropes have shown mixed success. Adenosine blockade with theophylline or aminophylline can sometimes be successful. Temporary and sometimes permanent pacing may be necessary in extreme circumstances.

PERMANENT PACEMAKER IMPLANTATION

Pacing in SA nodal disease is indicated to alleviate symptoms of bradycardia. Consensus guidelines published by the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) outline the indications for the use of pacemakers and categorize them by class based on levels of evidence (Fig. 251-6). Since the first implementation of permanent pacing in the 1950s, many advances in technology have resulted in miniaturization, increased longevity of pulse generators, improvement in leads, and increased functionality. To better understand

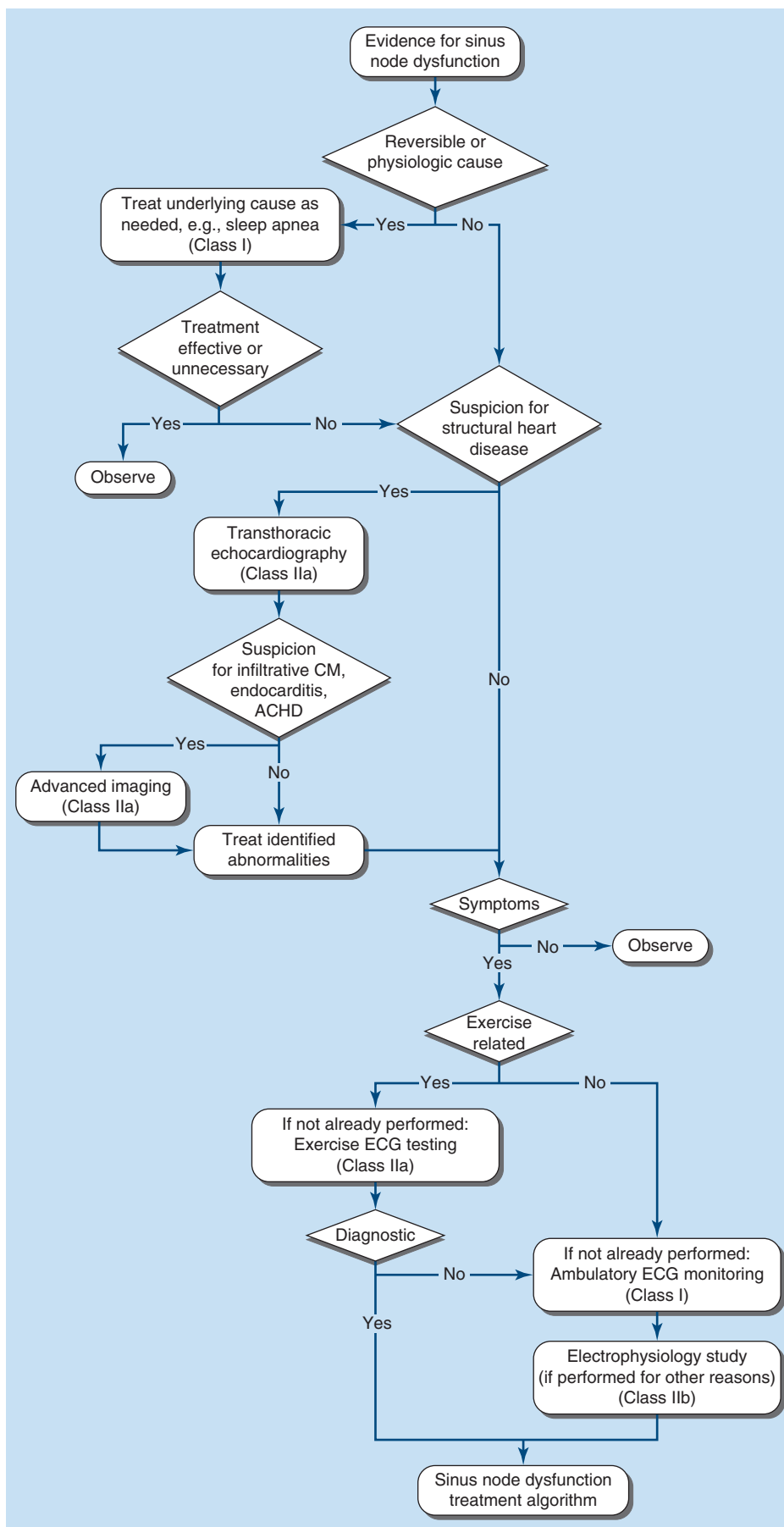


FIGURE 251-3 Evaluation of bradycardia and conduction disease. In patients with sinus node dysfunction, reversible causes should be identified and eliminated when possible. If no reversible cause can be identified, structural heart disease should be considered and evaluated for, if appropriate. If no symptoms are present, an observation strategy is appropriate. In patients who are symptomatic, further evaluation with ambulatory monitoring or exercise testing to identify symptom-rhythm correlation should be considered. ACHD, adult congenital heart disease; CM, cardiomyopathy. (Reproduced with permission from FM Kusumoto et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Heart Rhythm* 16:e128, 2019.)

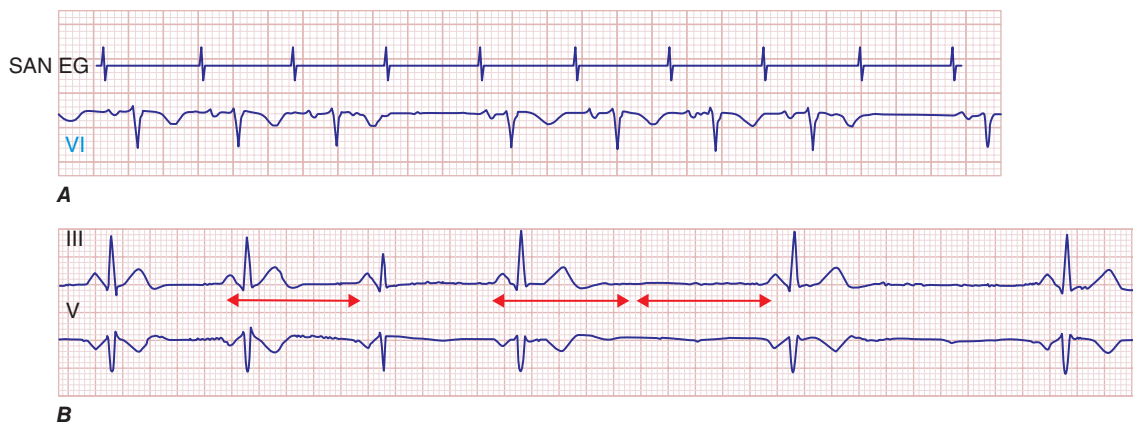


FIGURE 251-4 **A.** Mobitz type I sinoatrial (SA) nodal exit block. A theoretical SA node electrogram (SAN EG) is shown. Note that there is grouped beating producing a regularly irregular heart rhythm. The SAN EG rate is constant with progressive delay in exit from the node and activation of the atria, inscribing the P wave. This produces subtly decreasing P-P intervals before the pause, and the pause is less than twice the cycle length of the last sinus interval. **B.** Mobitz type II SA nodal exit block. This panel shows sinus rhythm in the first four beats followed by a sinus pause with the absence of a P wave. The interval comprising the absent P wave is exactly twice as long as the preceding P-P interval consistent with type II SA exit block.

pacemaker therapy for bradycardias, it is important to be familiar with the fundamentals of pacemaker function.

There is no established heart rate below which pacemaker treatment is indicated (Table 251-2). Well-conditioned athletes can have resting sinus rates below 40 beats/min, and some individuals can have similar levels of bradycardia during sleep. Permanent pacing is typically not indicated for sleep-related pauses felt secondary to high vagal tone in the absence of other symptoms. Asymptomatic sinus bradycardia has not been associated with adverse outcomes and does not typically warrant permanent pacing. In situations such as asymptomatic sinus bradycardia, sinus pauses secondary to physiologically elevated parasympathetic tone, transient pauses during sleep, or asymptomatic SND where symptoms have been documented to occur in the absence of bradycardia, a pacemaker is generally not indicated.

Medications to improve heart rate in order to avoid PPM are very rarely utilized. Medications such as methylxanthines (e.g., theophylline) or beta agonists (e.g., terbutaline) are sometimes utilized on

a temporary basis when a pacemaker may need to be delayed due to unique circumstances such as active infection. In addition, oral theophylline may be considered to determine if an increase in heart rate is associated with improvement in symptoms in a patient with sinus bradycardia to suggest that a PPM may be beneficial. This latter strategy is rarely utilized in more equivocal situations.

PPM is the principal treatment for SND, and the decision to pursue this treatment is largely driven by a correlation between symptoms and bradycardia. The stronger the correlation between symptoms and bradycardia, the greater is the likelihood of improvement. PPM is most commonly achieved through transvenous implantation of one or more leads through the left or right subclavian veins into the cardiac chambers. The leads are attached to a pacemaker generator that is placed subcutaneously in the pectoral chest region. Less commonly, pacing leads can be placed in the epicardium via surgical approaches including sternotomy or thoracotomy. This latter approach can be accomplished as a stand-alone procedure but is more commonly performed concomitantly

Termination of Atrial Fibrillation (90-105 bpm), Pause (7.4 seconds)

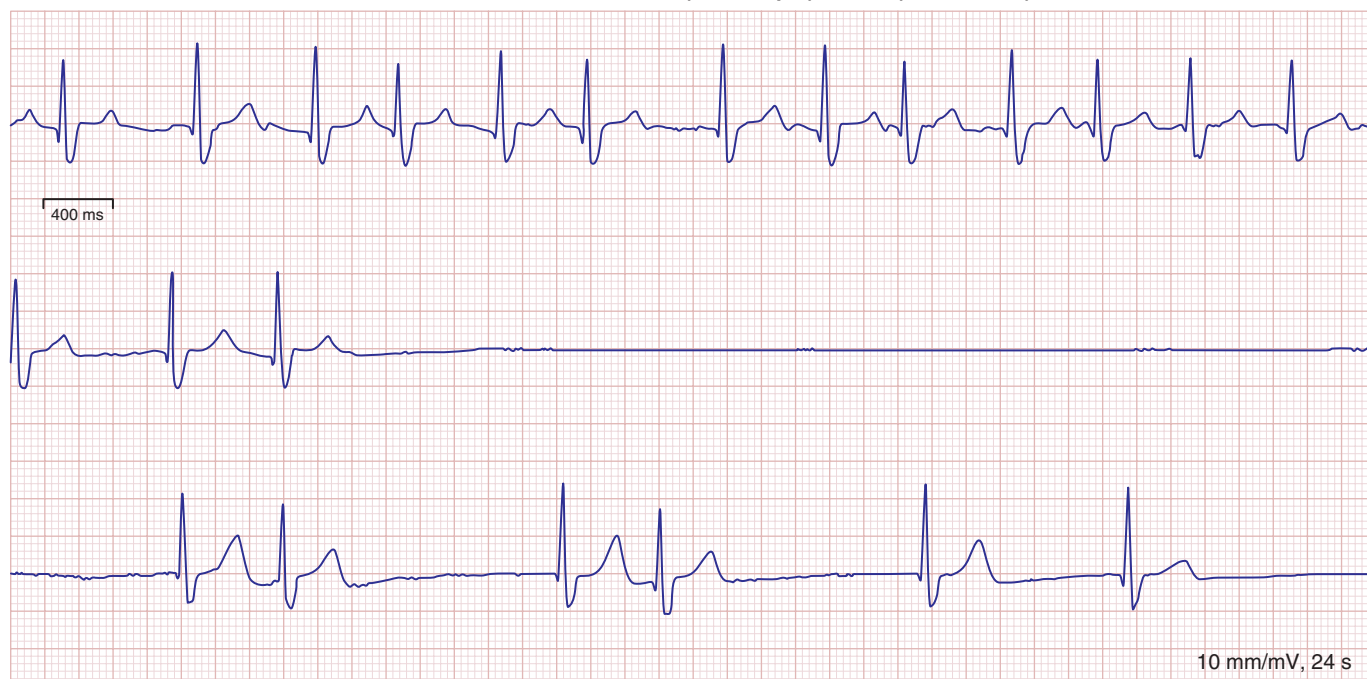


FIGURE 251-5 **Offset pause and tachy-brady syndrome.** An offset pause after termination of atrial fibrillation is seen and is consistent with tachy-brady syndrome.

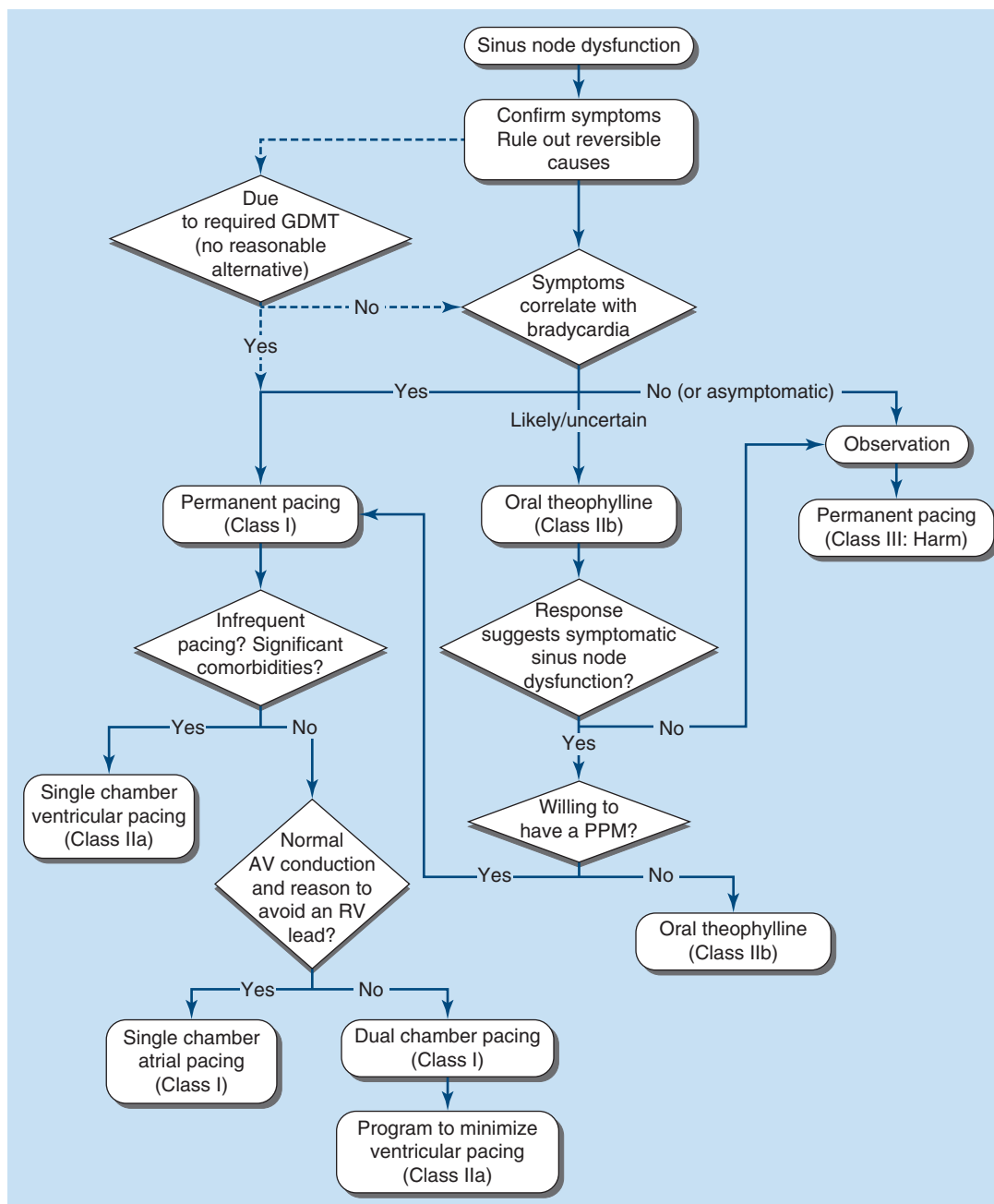


FIGURE 251-6 Management of sinus node dysfunction. Management of sinus node dysfunction begins with eliminating reversible causes and confirming whether symptoms correlate with bradycardia. If symptoms are clearly correlated, permanent pacing should be offered. If it is unclear, a trial of oral theophylline can be considered diagnostically. If there is no correlation between symptoms and bradycardia, then observation is appropriate. Class I recommendations should be performed or are indicated. Class IIa recommendations are considered reasonable to perform. Class IIb recommendations may be considered. Class III recommendations are associated with harm more than benefit. AV, atrioventricular; GDMT, guideline-directed management and therapy; PPM, permanent pacemaker; RV, right ventricular. (Reproduced with permission from FM Kusumoto et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Heart Rhythm* 16:e128, 2019.)

TABLE 251-2 Indications for Permanent Pacing in Sinus Node Dysfunction (SND)

- Symptoms that are directly attributable to SND
- Symptomatic sinus bradycardia because of essential medication therapy for which there is no alternative treatment
- Tachy-brady syndrome and symptoms attributable to bradycardia
- Symptomatic chronotropic incompetence
- In patients with symptoms that are possibly attributable to SND, a trial of oral theophylline may be considered to increase heart rate and determine if permanent pacing may be beneficial

Source: FM Kusumoto et al: *Heart Rhythm* 16:e128, 2019.

during another primary cardiac surgery. Leadless pacemakers that are totally self-contained pacing devices can also be placed in the right atrium and right ventricle to provide dual chamber pacing. Some leadless pacemakers can also incorporate technology to sense atrial activity to attempt to coordinate atrial sensing with ventricular pacing.

A standard nomenclature for pacing mode programming utilizes a four-letter code. The first letter indicates the chamber(s) paced (O, none; A, atrium; V, ventricular; D, dual; S, single). The second letter indicates the chamber(s) sensed. The third letter is the response to a sensed event (O, none; I, inhibited; T, triggered;

D, inhibition and triggered). The fourth letter refers to whether rate response (R) is turned on. Therefore, a dual-chamber pacemaker programmed in a DDDR mode provides atrial and ventricular pacing, A and V sensing, can be inhibited or triggered by a sensed beat, and is programmed to provide rate responsiveness to activity via either a built-in accelerometer, minute ventilation sensor, or both. Rate response is essential for the treatment of CI as it attempts to mimic the natural physiologic increase in heart rate in response to exertion.

A single-chamber atrial pacemaker can be a consideration in patients with pure SND who are felt to be at low risk for developing AV nodal block. However, fibrosis of the sinus node is associated with fibrosis of the AV node on pathology series in older patients and many patients with SND will develop AV node disease. Therefore, although a single-chamber atrial pacemaker can be a consideration in younger patients with pure SND, a majority of patients receiving a pacemaker for sinus node disease (particularly older individuals) often receive a dual-chamber pacemaker with backup ventricular pacing if needed.

Class I indications for pacing in SA node dysfunction include documented symptomatic bradycardia, SND-associated long-term drug therapy for which there is no alternative, and symptomatic CI. Class IIa indications include those outlined previously in which SND is suspected but not documented and for syncope of unexplained origin in the presence of major abnormalities of SA node dysfunction. Mildly symptomatic individuals with heart rates consistently <40 beats/min constitute a class IIb indication for pacing. Pacing is not indicated in patients with SA node dysfunction who do not have symptoms and in those in whom bradycardia is associated with the use of nonessential drugs.

COMPLICATIONS RELATED TO PACEMAKER IMPLANTATION

Although pacemakers are highly reliable, they are subject to a number of complications related to implantation and electronic function. In adults, permanent pacemakers are most commonly implanted with access to the heart by way of the subclavian superior vena cava venous system. Rare but possible acute complications of transvenous pacemaker implantation include infection, hematoma, pneumothorax, cardiac perforation, diaphragmatic/phrenic nerve stimulation, and lead dislodgment. Limitations of chronic pacemaker therapy include infection, erosion, lead failure, and abnormalities resulting from inappropriate programming or interaction with the patient's native electrical cardiac function. Rotation of the pacemaker pulse generator in its subcutaneous pocket, either intentionally or inadvertently, often referred to as "twiddler's syndrome," can wrap the leads around the generator and produce dislodgment with failure to sense or pace the heart. The small size and light weight of contemporary pacemakers make this a rare complication. Transvenous leads are considered the least reliable component of permanent pacing systems. Enhancements in battery technology and component design have produced a pacing system small enough to be implanted in the heart without the need for a transvenous lead. The first "leadless" pacemakers were only appropriate for patients with indications for single-chamber ventricular (right ventricle) pacing. More recently, these devices have been modified to detect mechanical atrial contraction and thus can be programmed to preserve AV synchrony in patients with heart block but without SND. Dual-chamber leadless pacemakers can also be implanted to preserve AV synchrony in patients with AV block.

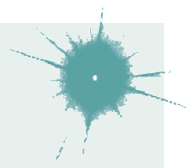
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252

The Bradyarrhythmias: Disorders of the Atrioventricular Node

William H. Sauer, Bruce A. Koplan



Impulses generated in the sinoatrial (SA) node are conducted to the ventricles through the electrically and anatomically complex atrioventricular (AV) node. The AV node is specialized for slow conduction of the action potential to create a delay between atrial and ventricular activation. There is a similar pattern of arrangement of gap junctions and expression of connexins in the AV node as in the sinus node. This allows for weak electrical coupling in the center of the node to slow conduction and protect it from the periphery. This unique arrangement of gap junctions, along with extracellular matrix and fibroblasts and a lack of conductance in adjacent valvular tissue, allow the AV node to slow conduction and serve as the electrical "gatekeeper" to the ventricle.

As described in previous chapters, cells located in the AV node sit at a relatively higher resting membrane potential than surrounding atrial and ventricular myocytes, exhibit spontaneous depolarization during phase 4 of the action potential, and have slower phase 0 depolarization (mediated by calcium influx in nodal tissue with a lack of the type of fast sodium channels found in atrial and ventricular myocytes) compared to ventricular tissue (mediated by sodium influx). Although the AV node has the potential for pacemaker activity, the normal automaticity rate is 20–60 beats/min, which is overridden by the higher intrinsic rate of the SA node (60–100 beats/min). Therefore, the AV node can provide a backup heart rate when the SA node fails to depolarize. There is a progressive decrease in the frequency of spontaneous depolarization down the His and Purkinje fibers. This progressive decrease in rate of depolarization allows for unidirectional flow of impulses through the conduction system.

Bradycardia may occur when conduction across the AV node is compromised, resulting in slow ventricular rates. The consequences can be fatigue, syncope, and, if a reliable escape rhythm does not occur, death from asystole. Transient AV conduction block is common in the young and is most likely the result of high vagal tone found in up to 10% of young adults. Acquired and persistent failure of AV conduction is rare in healthy adult populations, with an estimated incidence of 1 per 5000 in the U.S. population per year. In the setting of myocardial ischemia, aging and fibrosis, or cardiac infiltrative diseases, however, persistent AV block is much more common. As with symptomatic bradycardia arising from SA node dysfunction, permanent pacing is the only reliable therapy for symptoms arising from AV conduction block. While pacemakers for sinus node dysfunction are mainly indicated when symptoms correlate with bradycardia, pacemakers may be indicated in some forms of AV block in the absence of symptoms if the type of AV block is lower in the conduction system (infra-Hisian block) due to an increased risk of life-threatening asystole even if symptoms are not present leading up to such an event.

STRUCTURE AND PHYSIOLOGY OF THE AV NODE

The normal AV junctional area can be divided into a transition cell zone (which results from approaches from the atrium to the AV node), the compact AV node, and the penetrating part of the His bundle. Conduction from the SA node to the AV node occurs in a preferential manner via intra-atrial pathways with higher conduction velocity than the remainder of atrial tissue. The AV node itself is a small region (~1 × 3 × 5 mm) that lies beneath the right atrial endocardium at the apex of the triangle of Koch, a region defined by three landmarks: the coronary sinus ostium posteriorly, the septal tricuspid valve annulus anteriorly, and the tendon of Todaro superiorly. The AV node can be further

subdivided into the lower nodal bundle and compact node. A rightward inferior node extension spreads along the tricuspid valve toward the coronary sinus, and the leftward nodal extension spreads from the compact node along the tendon of Todaro. In some people, there are two functional pathways in the AV node: a slow pathway located in the inferior node extension and a fast pathway that is less well defined but is superior to the slow pathway. The role of these pathways in supraventricular tachycardia is described in another chapter.

The compact AV node continues anteriorly and superiorly as the penetrating AV bundle where it traverses the central fibrous body in close proximity to the aortic, mitral, and tricuspid valve annuli. The penetrating AV bundle continues through the annulus fibrosis and emerges as the His bundle along the ventricular septum. The right bundle branch (RBB) emerges from the distal AV bundle and terminates to a band that traverses the right ventricle (moderator band). In contrast, the left bundle branch (LBB) is a broad subendocardial sheet of tissue on the septal left ventricle. The Purkinje fiber network emerges from the RBB and LBB and extensively ramifies on the endocardial surfaces of the right and left ventricles, respectively.

The cells that constitute the AV node complex are heterogeneous with a range of action potential profiles. The AV junction has distinct regions including a transitional cell zone (atrionodal cells), the compact AV node, and the cells of the penetrating part of the His bundle. In the transitional zones, the cells have an electrical phenotype between those of atrial myocytes and cells of the compact node. Atrionodal transitional connections exhibit *decremental conduction*, defined as slowing of conduction with increasingly rapid rates of stimulation. Myocytes that constitute the compact AV node are similar to sinus node myocytes, having a resting membrane potential of ~ -60 mV; exhibit action potentials with low amplitudes, slow upstrokes of phase 0 (<10 V/s), and spontaneous phase 4 diastolic depolarization; and have high-input resistance and relative insensitivity to external $[K^+]$. The action potential phenotype is explained by the complement of ionic currents expressed. AV nodal cells lack a robust inward rectifier potassium current (I_{K1}) and fast sodium current (I_{Na}); L-type calcium current (I_{Ca-L}) is responsible for phase 0; and phase 4 depolarization reflects the composite activity of the depolarizing currents—funny current (I_f), I_{Ca-T} , T-type calcium current (I_{Ca-T}), and sodium-calcium exchanger current (I_{NCX})—and the repolarizing currents—delayed rectifier (I_{Kr}) and acetylcholine-gated (I_{KACH}) potassium currents. Electrical coupling between cells in the AV node is tenuous due to the relatively sparse expression of gap junction channels (predominantly connexin-40) and increased extracellular volume.

The His bundle and the bundle branches are insulated from ventricular myocardium. The most rapid conduction in the heart is observed in Purkinje cells (1–3 m/s), with action potentials exhibiting a very rapid upstroke (phase 0), prolonged plateau (phase 2), and modest automaticity (phase 4 depolarization). Gap junctions, composed largely of connexin-40, are abundant, but bundles are not connected transversely to ventricular myocardium. The AV node is innervated by both sympathetic and parasympathetic autonomic input that can either slow or enhance conduction.

The blood supply to the penetrating AV bundle is from the AV nodal artery and first septal perforator of the left anterior descending coronary artery. The AV node artery arises from the right coronary artery (80–90% of the time) or the left circumflex (10%) with the assigned artery associated with the dominance of the coronary artery circulation. The bundle branches also have a dual blood supply from the septal perforators of the left anterior descending coronary artery (LBB and proximal RBB) and branches of the posterior descending coronary artery. The AV node is highly innervated with postganglionic sympathetic and parasympathetic nerves; however, the bundle of His and distal conducting system are not influenced by autonomic tone.

ELECTROCARDIOGRAPHIC DEFINITIONS OF AV CONDUCTION BLOCK (TABLE 252-1)

Conduction block in the AV node is classified based on the appearance on electrocardiography (ECG), which may also be a reflection of the location of block along the AV conduction axis. First-degree AV block

TABLE 252-1 Electrocardiographic Classification of Atrioventricular (AV) Block

First-Degree AV Block

All atrial impulses are conducted to the ventricle
PR interval is abnormally long (>200 ms)
AV delay usually occurs within the AV node

Second-Degree AV Block (intermittent failure of conduction between atrium and ventricle)

Two subtypes

Type I/Mobitz I/Wenckebach block: progressive prolongation of the PR interval until loss of conduction occurs
Type II/Mobitz II: fixed PR interval precedes loss of conduction
Usually associated with QRS widening

Third-Degree AV Block (complete heart block)

Complete interruption of conduction between atria and ventricles

involves a fixed prolongation of the PR interval (>200 ms). In first-degree AV block, delay usually occurs within the AV node, although the atria, His bundle, and Purkinje system may also be involved. Although the term *block* is a misnomer of sorts because electrical conduction is delayed and not interrupted, it remains commonly in use. Second-degree AV block involves intermittent failure of conduction between the atrium and ventricle. There are two subtypes of second-degree AV block. Type I (Mobitz I, Wenckebach) AV block manifests as progressive prolongation of the PR interval prior to one or more “dropped” QRS complexes. Progressive shortening of the RR interval and grouped beating of QRS complexes are classically seen in Mobitz I AV block. In addition, comparison of the last PR interval before and the first PR interval after the absent QRS complex will often reveal the greatest discrepancy of PR interval, making the diagnosis of Mobitz I AV block most evident. Mobitz I AV block typically involves the AV node, is hemodynamically stable, and in the absence of symptoms, does not typically warrant pacing. Type II second-degree AV block manifests on ECG as failed AV conduction preceded by fixed PR interval (no prolongation of PR interval prior to a dropped beat). Type II block has more serious implications, including a risk of sudden death. It is infranodal in location and associated with a less reliable escape rhythm, and thus, permanent pacing is required even in the absence of symptoms. In the setting of 2:1 AV block, ECG differentiation of type I versus type II block is not possible. If the PR interval is <160 ms prior to the AV conduction and QRS is wider than normal, infranodal (type II) block is most likely. Complete heart block (third-degree block) involves complete AV dissociation with a ventricular rate that is slower than the atrial rate (Fig. 252-1).

In the absence of a preexisting bundle branch block, a wide QRS escape rhythm implies a block in the distal His or bundle branches; in contrast, a narrow QRS rhythm implies a block in the AV node or proximal His and an escape rhythm originating in the AV junction. Narrow QRS escape rhythms are typically faster and more stable than wide QRS escape rhythms and originate more proximally in the AV conduction system.

ETIOLOGY OF AV CONDUCTION DISEASE

There are numerous causes of intrinsic AV node dysfunction. Fibrosis and sclerosis of the conduction system are the most common causes of acquired conduction disease, accounting for $\sim 50\%$ of AV block. Numerous conditions that may not be distinguishable from one another can lead to conduction system fibrosis. Senile degeneration of the conduction system is most commonly seen in the elderly and results from idiopathic fibrosis and calcification. Lev's disease results from proximal bundle branch fibrosis. Lenègre's disease results from a sclerodegenerative process that occurs in a younger age group and involves the more distal portions of the bundle branches. Calcification of the aortic valve annulus can encroach on the conduction system. Compared to aortic valve calcification, mitral calcification is less commonly a cause of AV block (Table 252-2).

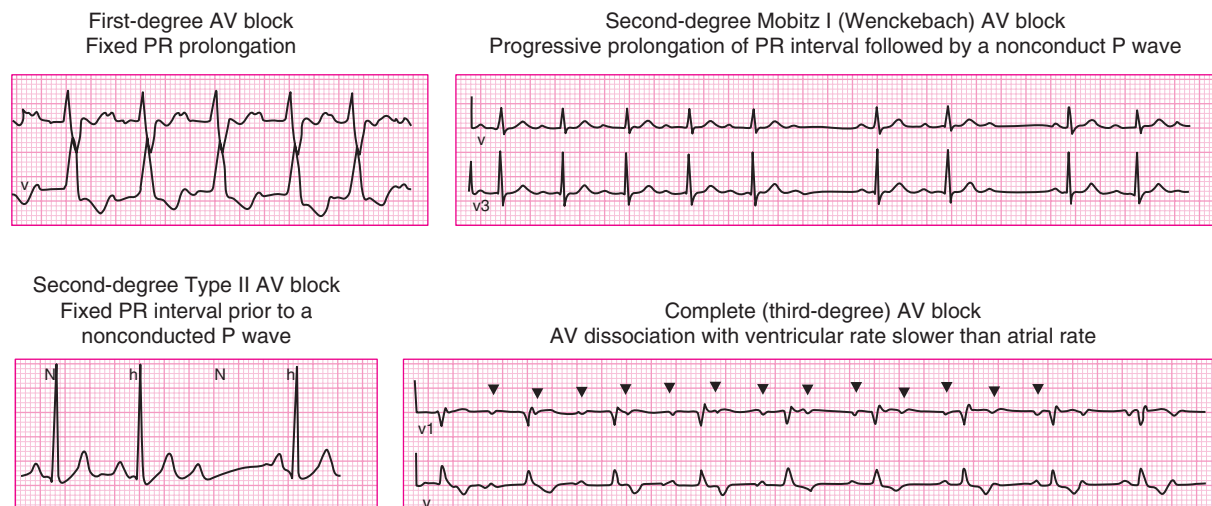


FIGURE 252-1 Types of atrioventricular (AV) block. The *upper left* figure displays fixed prolongation of the PR interval. The *upper right* figure demonstrates Mobitz I block (Wenckebach AV block) manifested as progressive prolongation of the PR interval followed by a nonconducted P wave ("dropped beat"). The *lower left* figure displays AV block with P wave with no QRS complex and no associated PR prolongation prior to the dropped beat (Mobitz type II AV block). The *lower right* figure demonstrates complete heart block manifested as dissociation between P waves and QRS complexes (AV dissociation).

■ IATROGENIC CAUSES

AV block may also be from iatrogenic causes. Cardiac surgery, most commonly cardiac valve surgery, can result in damage to the AV conduction system, with the highest risk occurring in aortic valve and tricuspid valve surgery. Percutaneous transcatheter aortic valve

replacement, septal myectomy, and alcohol septal ablation also carry a risk of AV block. Percutaneous catheter ablation for atrial arrhythmias, particularly AV nodal reentry tachycardia ablation, is associated with a small (<1%) risk of AV block. Medications, including beta blockers, verapamil, diltiazem, and digoxin, are also common iatrogenic causes of AV block. Many patients with drug-induced AV block have preexisting conduction system disease. Iatrogenic AV block may occur rarely in the setting of thoracic radiation or chemotherapy. AV block is a rare complication of the surgical repair of ventricular septal defects (VSDs) or atrial septal defects (ASDs) but may complicate repairs of transposition of the great arteries.

■ AV BLOCK IN THE SETTING OF MYOCARDIAL ISCHEMIA

Coronary artery disease may produce transient or persistent AV block. In the setting of coronary spasm, ischemia, particularly in the right coronary artery distribution, may produce transient AV block. In acute myocardial infarction (MI), AV block transiently develops in 10–25% of patients; most commonly, this is first- or second-degree AV block, but complete heart block (CHB) may also occur. Second-degree and higher-grade AV block tends to occur more often in inferior than in anterior acute MI; however, the level of block in inferior MI tends to be in the AV node with more stable, narrow escape rhythms. In contrast, acute anterior MI is associated with block in the distal AV nodal complex, His bundle, or bundle branches and results in wide complex, unstable escape rhythms and a worse prognosis with high mortality rates.

AV conduction abnormalities may be caused by either direct ischemia to the conduction system or enhanced autonomic tone (Bezold-Jarisch reflex). Conduction abnormalities can be considered based on infarct location, and this may also predict which conduction abnormalities may be reversible. High-grade AV block associated with inferior MI is often located proximal to the His bundle in 90% of patients. Narrow junctional escape typically occurs with rates >40 beats/min, and a temporary pacemaker is typically not required as the AV block is often reversible and successfully managed with pharmacologic therapy. High-grade AV block in the setting of anterior MI is typically indicative of extensive infarction, is more often distal to the AV node, and is associated with an increased mortality. Temporary pacing in this circumstance is typically indicated. CHB in the setting of anterior MI may also be preceded by RBB block due to the arterial supply of the proximal RBB.

■ INFECTIOUS CAUSES OF AV BLOCK

Infection can also cause AV block. AV block is a common manifestation of Lyme carditis due to infection with *Borrelia burgdorferi*.

TABLE 252-2 Causes of AV Block

Fibrosis/sclerosis/calcification of the conduction system
Senile degeneration of the conduction system (Lev's disease)
Lenègre's disease
Calcification of the aortic valve annulus (mitral—less common)
Iatrogenic
After cardiac surgery (including valve surgery)
TAVR/alcohol septal ablation
Complication from catheter ablation
Medication (beta blockers, verapamil, diltiazem, digoxin)
Toxin/overdose/poisoning
Acute MI/coronary ischemia
Infectious causes
Lyme carditis
Bacterial endocarditis with perivalvular abscess
Viral myocarditis
Chagas' disease
Toxoplasmosis
Infiltrative heart disease/inflammatory disease
Sarcoidosis
Amyloid
Rheumatologic disease: reactive arthritis (Reiter's syndrome), SLE, RA, systemic sclerosis
Congenital AV block
Maternal lupus
Idiopathic congenital AV block
Congenital heart defects
Genetic
Endocrine (e.g., thyroid disease, hypoadosteronism)
Autoimmune disease
Neuromuscular disease (e.g., myotonic dystrophy, Kearns-Sayre syndrome, Erb's dystrophy)
Lymphoma
Enhanced vagal tone/neurocardiogenic

Abbreviations: AV, atrioventricular; MI, myocardial infarction; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TAVR, transcatheter aortic valve replacement.

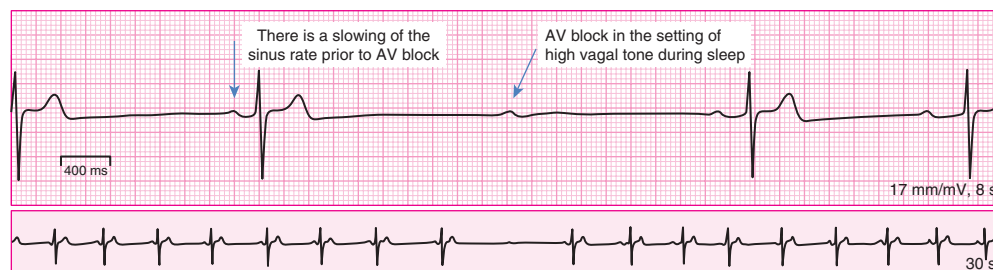


FIGURE 252-2 Evidence of atrioventricular (AV) block during sleep. During sleep, increased vagal tone leads to sinus bradycardia with associated Mobitz I (Wenckebach) AV block. See Fig. 252-1 for an explanation of Mobitz I block.

AV block is typically at the level of the AV node with narrow junctional escape rhythm >40 beats/min. Less commonly, conduction abnormalities can occur below the level of the AV node or in the sinus node. In Lyme carditis, AV block typically improves within 1 week of antibiotic therapy, although a longer time frame can occur in some patients. AV block in the setting of infective endocarditis should raise concern for perivalvular abscess, which requires urgent surgical consultation. Viral myocarditis, Chagas' disease, and toxoplasmosis are less common infectious causes of AV block. Infiltrative heart disease such as cardiac sarcoid, amyloid, and hemochromatosis can also present as AV block. Autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis, mixed connective tissue disease, and scleroderma, may cause AV block due to infiltration of the conduction system. Rare malignancies also may impair AV conduction.

■ AUTONOMIC AND FUNCTIONAL CAUSES OF AV BLOCK

Functional causes of AV block (autonomic, metabolic/endocrine, and drug-related) tend to be reversible. Most other etiologies produce structural changes, typically fibrosis, in segments of the AV conduction axis that are generally permanent. Heightened vagal tone during sleep or in well-conditioned individuals can be associated with all grades of AV block (Fig. 252-2).

Carotid sinus hypersensitivity, vasovagal syncope, and cough and micturition syncope may be associated with SA node slowing and AV conduction block. Transient metabolic and endocrinologic disturbances and a number of pharmacologic agents also may produce reversible AV conduction block.

■ ACQUIRED AV BLOCK FROM FIBROSIS AND INFILTRATIVE CARDIOMYOPATHIES

Idiopathic progressive fibrosis of the conduction system is one of the more common and degenerative causes of AV conduction block. Aging is associated with degenerative changes in the summit of the ventricular septum, central fibrous body, and aortic and mitral annuli and has been described as "sclerosis of the left cardiac skeleton." The process typically begins in the fourth decade of life and may be accelerated by atherosclerosis, hypertension, and diabetes mellitus. Accelerated forms of progressive familial heart block have been identified in families with mutations in the cardiac sodium channel gene (*SCN5A*) and other loci that have been mapped to chromosomes 1 and 19.

AV conduction block has been associated with heritable neuromuscular diseases, including the nucleotide repeat disease myotonic dystrophy, the mitochondrial myopathy Kearns-Sayre syndrome, and several of the monogenic muscular dystrophies. Patients with these neuromuscular diseases and evidence of AV block should be considered for permanent pacing support.

■ CONGENITAL AV BLOCK

Congenital AV block may be observed in complex congenital cardiac anomalies, such as transposition of the great arteries, ostium primum ASDs, VSDs, endocardial cushion defects, and some single-ventricle defects. Congenital AV block in the setting of a structurally normal heart can occur sporadically and can also be seen in children born to mothers with SLE and other autoimmune diseases.

DIAGNOSTIC TESTING

Patients with conduction abnormalities should be evaluated for the presence or absence of structural heart disease. Physical exam may reveal valvular heart disease. ECG may suggest concomitant disease that predisposes to conduction abnormalities. Echocardiography is also indicated to evaluate for structural heart disease including valvular abnormalities, ejection fraction, and ventricular wall motion. Because age-dependent progressive fibrosis of the conduction system is the most common cause, AV node block that develops at a younger age (≤ 60 years) warrants advanced imaging such as chest computed tomography (CT), cardiac magnetic resonance imaging (MRI), or CT/positron emission tomography (PET) scan to further evaluate for infiltrative heart disease such as sarcoidosis. Advanced imaging may also be warranted based on other factors in the history and testing that suggest the need for evaluation of infiltrative heart disease. Evaluation for cardiac ischemia should be driven by the clinical suspicion at presentation (e.g., symptoms of ischemia, ECG abnormalities, etc.) (Fig. 252-3).

Diagnostic testing in the evaluation of AV block is aimed at determining the level of conduction block, particularly in asymptomatic patients, since the prognosis and therapy depend on whether the block is in or below the AV node. Vagal maneuvers, carotid sinus massage, exercise, and administration of drugs such as atropine and isoproterenol may be diagnostically informative. Owing to the differences in the innervation of the AV node and infranodal conduction system, vagal stimulation and carotid sinus massage slow conduction in the AV node but have less of an effect on infranodal tissue and may even appear to improve conduction due to a reduced rate of activation of distal tissues. Conversely, atropine, isoproterenol, and exercise improve conduction through the AV node and may appear to impair infranodal conduction. In patients with congenital CHB and a narrow QRS complex, exercise typically increases heart rate; by contrast, those with acquired CHB, particularly with wide QRS, do not respond to exercise with an increase in heart rate.

Additional diagnostic evaluation, including electrophysiologic testing, may be indicated in patients with syncope and suspected high-grade AV block. This is particularly relevant if noninvasive testing does not reveal the cause of syncope or if the patient has structural heart disease with ventricular tachyarrhythmias as a cause of symptoms. Electrophysiologic testing provides more precise information regarding the location of AV conduction block and permits studies of AV conduction under conditions of pharmacologic stress and exercise. Recording of the His bundle electrogram by a catheter positioned at the superior margin of the tricuspid valve annulus provides information about conduction at all levels of the AV conduction axis. A properly recorded His bundle electrogram reveals local atrial activity, the His electrogram, and local ventricular activation; when it is monitored simultaneously with recorded body surface ECG traces, intra-atrial, AV nodal, and infranodal conduction times can be assessed. The time from the most rapid deflection of the atrial electrogram in the His bundle recording to the His electrogram (*AH interval*) represents conduction through the AV node and is normally <130 ms. The time from the His electrogram to the earliest onset of the QRS on the surface ECG (*HV interval*) represents the conduction time through the His-Purkinje system and is normally ≤ 55 ms (Fig. 252-4).

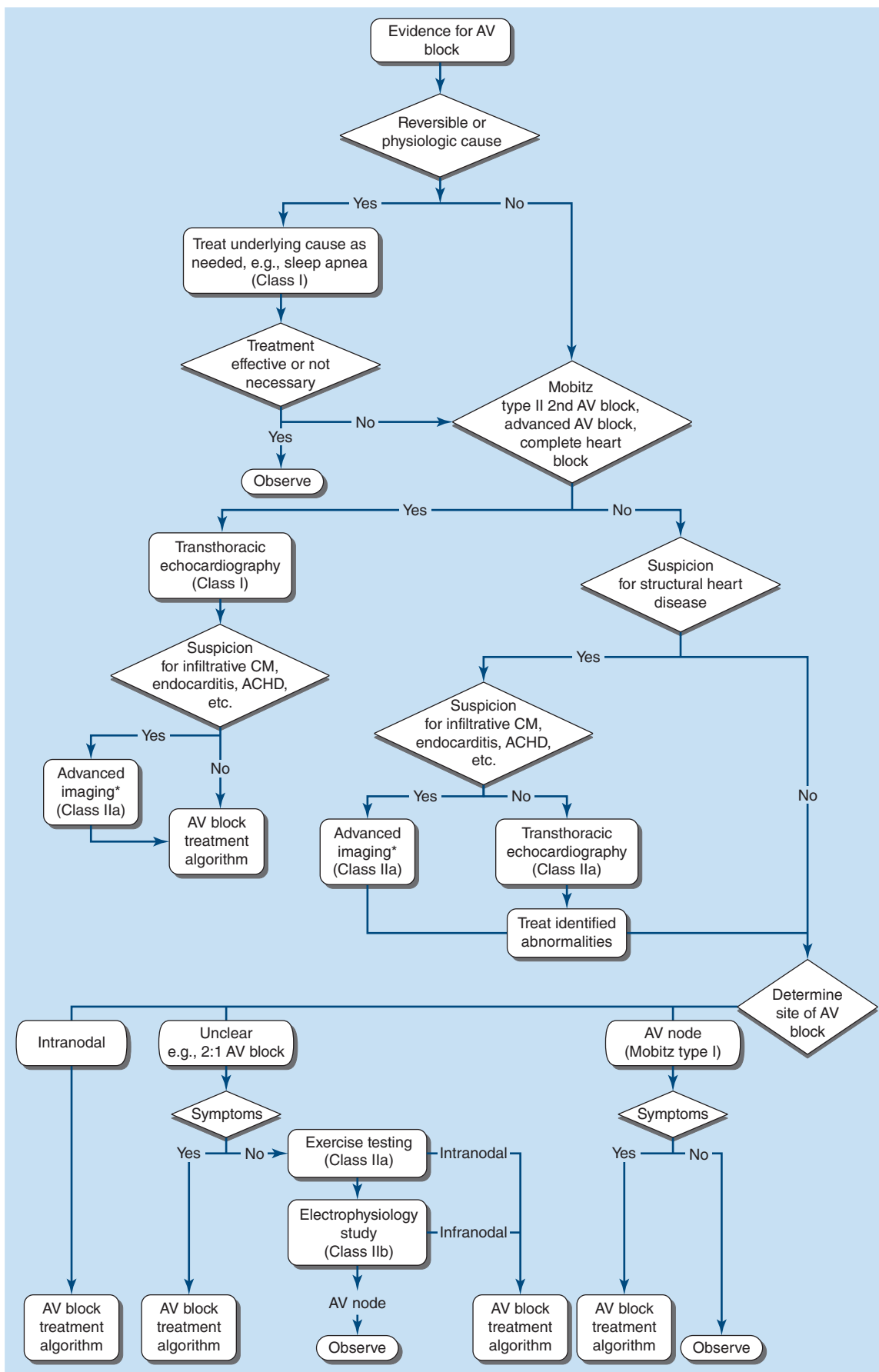


FIGURE 252-3 Initial evaluation of suspected atrioventricular (AV) block algorithm. *Targeted advanced imaging—magnetic resonance imaging (MRI): amyloidosis, myocarditis, hemochromatosis, sarcoidosis, congenital heart disease (CHD), sinus of Valsalva aneurysm, aortic dissection, arrhythmogenic right ventricular cardiomyopathy; fluorodeoxyglucose-positron emission tomography (FDG-PET): sarcoidosis; technetium-99m pyrophosphate (Tc PYP) or 99m technetium 3,3-diphosphono-1,2-propanodicarboxylic acid (TC-DPD): transthyretin (TTR) amyloidosis; cardiac computed tomography (CT): CHD, sinus of Valsalva. ACHD, adult CHD; CM, cardiomyopathy. (Reproduced with permission from FM Kusumoto et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Heart Rhythm* 16:e128, 2019.)

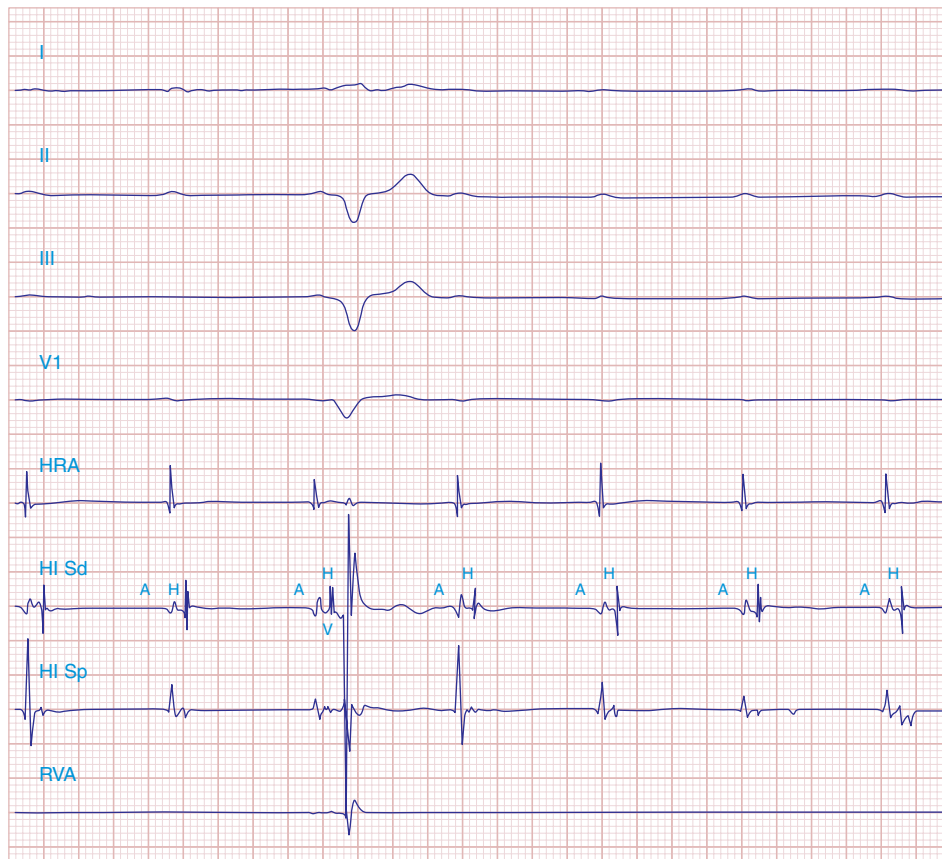


FIGURE 252-4 High-grade atrioventricular (AV) block below the His. The AH interval is normal and is not changing before the block. Atrial and His bundle electrograms are recorded consistent with block below the distal AV junction. I, II, III, and V₁ are surface electrocardiogram leads. HISp, HISd, and RVA are the proximal HIS, distal HIS, and right ventricular apical electrical recordings, respectively. A, H, and V represent the atrial, His, and ventricular electrograms on the His bundle recording, respectively. (Courtesy of Dr. Joseph Marine.)

Rate stress produced by pacing can unmask abnormal AV conduction. Mobitz I second-degree AV block at short atrial paced cycle lengths is a normal response. However, when it occurs at atrial cycle lengths >500 ms (<120 beats/min) in the absence of high vagal tone, it is abnormal. Typically, type I second-degree AV block is associated with prolongation of the AH interval, representing conduction slowing and block in the AV node. AH prolongation occasionally is due to the effect of drugs (beta blockers, calcium channel blockers, digitalis) or increased vagal tone. Atropine can be used to reverse high vagal tone; however, if AH prolongation and AV block at long pacing cycle lengths persist, intrinsic AV node disease is likely. Type II second-degree block is typically infranodal, often in the His-Purkinje system. Block below the node with prolongation of the HV interval or a His bundle electrogram with no ventricular activation is abnormal unless it is elicited at fast pacing rates or short coupling intervals with extra stimulation. It is often difficult to determine the type of second-degree AV block when 2:1 conduction is present; however, the finding of a His bundle electrogram after every atrial electrogram indicates that block is occurring in the distal conduction system.

Intracardiac recording at an electrophysiologic study that reveals prolongation of conduction through the His-Purkinje system (i.e., long HV interval) is associated with an increased risk of progression to higher grades of block and is generally an indication for pacing. In the setting of bundle branch block, the HV interval may reveal the condition of the unblocked bundle and the prognosis for developing more advanced AV conduction block. Prolongation of the HV interval in patients with asymptomatic bundle branch block is associated with an increased risk of developing higher-grade AV block. The risk increases with greater prolongation of the HV interval such that in patients with an HV interval >100 ms, the annual incidence of complete AV block approaches 10%, indicating a need for pacing. In patients with acquired CHB, even if intermittent, there is little role for electrophysiologic testing, and pacemaker implantation is almost always indicated.

TREATMENT

Acute Management of AV Conduction Block

The first-line strategies for management of AV block should be to eliminate reversible causes and to determine the immediate safety and reliability of the heart rhythm (e.g., escape rhythm) and whether or not temporary or permanent pacing is warranted. The need for temporary pacing is determined by the symptoms of the patient, hemodynamic status, and the estimate of the level at which AV block is present. In a general sense, the lower in the conduction system that an escape rhythm is occurring, the lower is the reliability of the escape rhythm. A narrow-complex junctional escape of 45 beats/min with no symptoms does not warrant urgent temporary pacing, whereas a wide-complex (implying block lower in the conduction system) escape rhythm at 30 beats/min does. Elimination of unnecessary medications known to slow AV conduction (e.g., beta blockers, diltiazem, verapamil, digoxin), correction of electrolyte abnormalities, ischemia, and inhibition of excessive vagal tone may increase the heart rate. Adjunctive pharmacologic treatment with atropine or isoproterenol may be useful if the block is in the AV node. When pacing is indicated, the most expeditious technique is the use of transcutaneous pacing, where pacing patches are placed anteriorly over the cardiac apex (cathode) and posteriorly between the spine and the scapula or above the right nipple (anode). Acutely, transcutaneous pacing is highly effective, but its duration is limited by patient discomfort and longer-term failure to capture the ventricle owing to changes in lead impedance. Transvenous temporary pacing is more reliable, and a pacing wire can be placed from the jugular, subclavian, or femoral venous system and advanced to the right ventricle, permitting stable temporary pacing.

AV conduction abnormalities may be reversible in certain circumstances including removal of unnecessary medication or toxins,

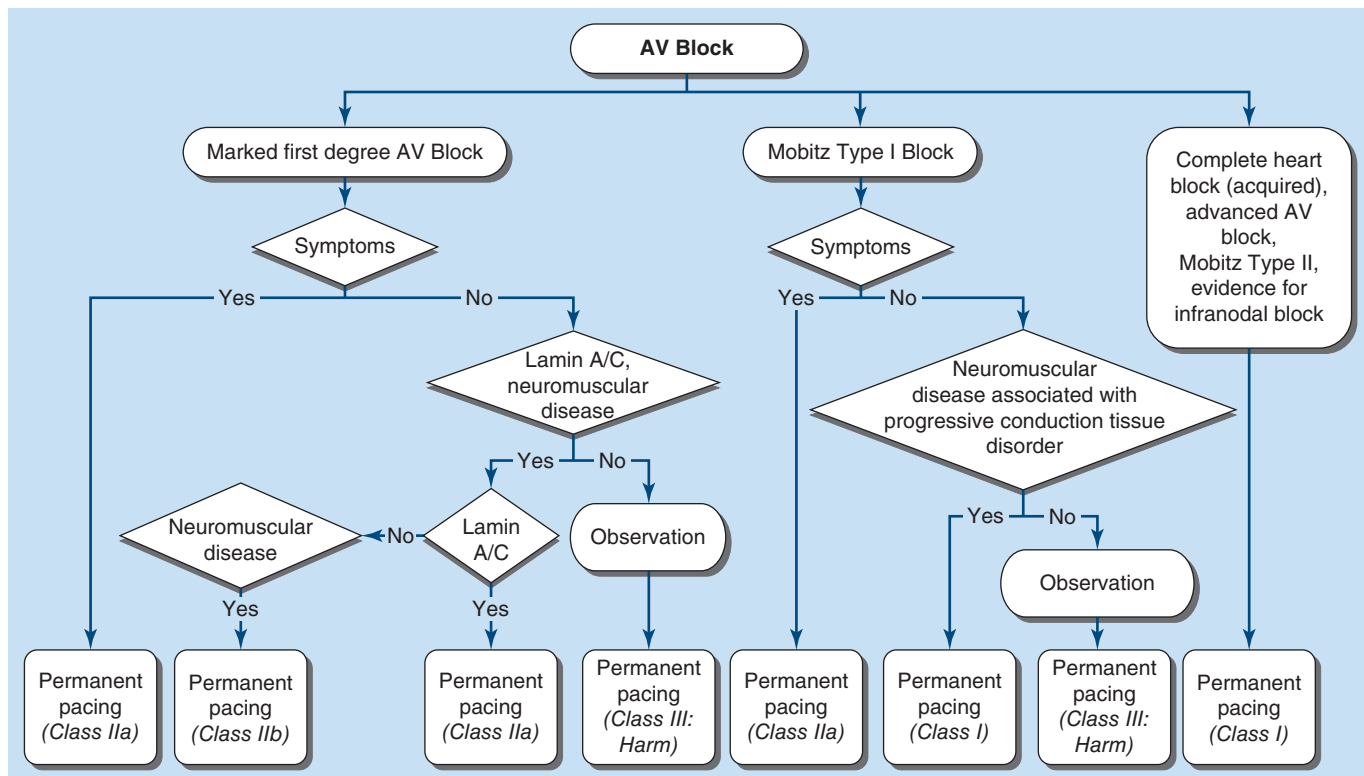


FIGURE 252-5 Indications for pacing in patients with atrioventricular (AV) block. In patients presenting with AV block, the category of AV block should be determined (first-degree, second-degree, or complete heart block). In first-degree AV block, permanent pacing may be indicated in the setting of symptoms or higher-risk systemic disease such as neuromuscular disease or Lamin A/C cardiomyopathy. In Mobitz I AV block, pacing may be considered in the setting of symptoms or the additional disease mentioned with first-degree AV block. In complete heart block or Mobitz II AV block, permanent pacing is generally indicated. Class I recommendations should be performed or are indicated. Class IIa recommendations are considered reasonable to perform. Class IIb recommendations may be considered. Class III recommendations are associated with harm more than benefit. (Reproduced with permission from FM Kusumoto et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. *Heart Rhythm* 16:e128, 2019.)

correction of electrolyte abnormalities, relief of ischemia, treatment of certain infiltrative heart disease (e.g., immunosuppression in cardiac sarcoidosis), and treatment of sleep apnea in patients with nocturnal vagally mediated AV block. When symptomatic or infranodal AV block is not reversible, which is often the case, permanent pacing is warranted.

PERMANENT PACEMAKER IMPLANTATION

The indications for pacing in AV conduction block are shown in Fig. 252-5. In patients with acquired Mobitz type II AV block, high-grade AV block, or third-degree AV block that is not reversible or physiologic, permanent pacing is recommended regardless of symptoms. For all other types of AV block, in the absence of conditions associated with progressive AV conduction abnormalities, permanent pacing should generally be considered only in the presence of symptoms that correlate with block. In patients with neuromuscular disease and other progressive cardiomyopathies affecting the conduction system, permanent pacemaker implantation is recommended for marked first-degree AV block and Mobitz I AV block. Pacemaker implantation should be performed in any patient with symptomatic bradycardia and irreversible second- or third-degree AV block, regardless of the cause or level of block in the conducting system. Symptoms may include those directly related to bradycardia and low cardiac output or to worsening heart failure, angina, or intolerance to an essential medication. Pacing in patients with asymptomatic AV block should be individualized; situations in which pacing should be considered are patients with acquired CHB, particularly in the setting of cardiac enlargement; left ventricular dysfunction; and waking heart rates ≤ 40 beats/min. Patients who have asymptomatic second-degree AV block of either type should be considered for pacing if the block is demonstrated to be intra- or infra-His or is associated with a wide QRS complex. Pacing may be indicated in asymptomatic patients in special circumstances, in patients with profound first-degree AV block and left ventricular dysfunction in whom a shorter AV interval produces hemodynamic

improvement, and in the setting of milder forms of AV conduction delay (first-degree AV block, intraventricular conduction delay) in patients with neuromuscular diseases that have a predilection for the conduction system, such as myotonic dystrophy and other muscular dystrophies and Kearns-Sayre syndrome.

AV block in acute MI is often transient, particularly in inferior infarction. The circumstances in which pacing is indicated in acute MI are persistent second- or third-degree AV block, particularly if symptomatic, and transient second- or third-degree AV block associated with bundle branch block. Pacing is generally not indicated in the setting of transient AV block in the absence of intraventricular conduction delays or in the presence of fascicular block or first-degree AV block that develops in the setting of preexisting bundle branch block. Fascicular blocks that develop in acute MI in the absence of other forms of AV block also do not require pacing.

Distal forms of AV conduction block may require pacemaker implantation in certain clinical settings. Patients with bifascicular or trifascicular block and symptoms, particularly syncope that is not attributable to other causes, should undergo pacemaker implantation. Permanent pacemaker implantation is indicated in asymptomatic patients with bifascicular or trifascicular block who experience intermittent third-degree block, type II second-degree AV block, or alternating bundle branch block. In patients with fascicular block who are undergoing electrophysiologic study, a markedly prolonged HV interval or block below the His at long cycle lengths also may constitute an indication for permanent pacing. Patients with fascicular block and the neuromuscular diseases previously described should also undergo pacemaker implantation.

SELECTION OF PACING MODE AND SYSTEM

In general, a pacing mode that maintains AV synchrony reduces complications of pacing such as pacemaker syndrome and pacemaker-mediated tachycardia. This is particularly true in younger patients; the importance of dual-chamber pacing in the elderly, however, is

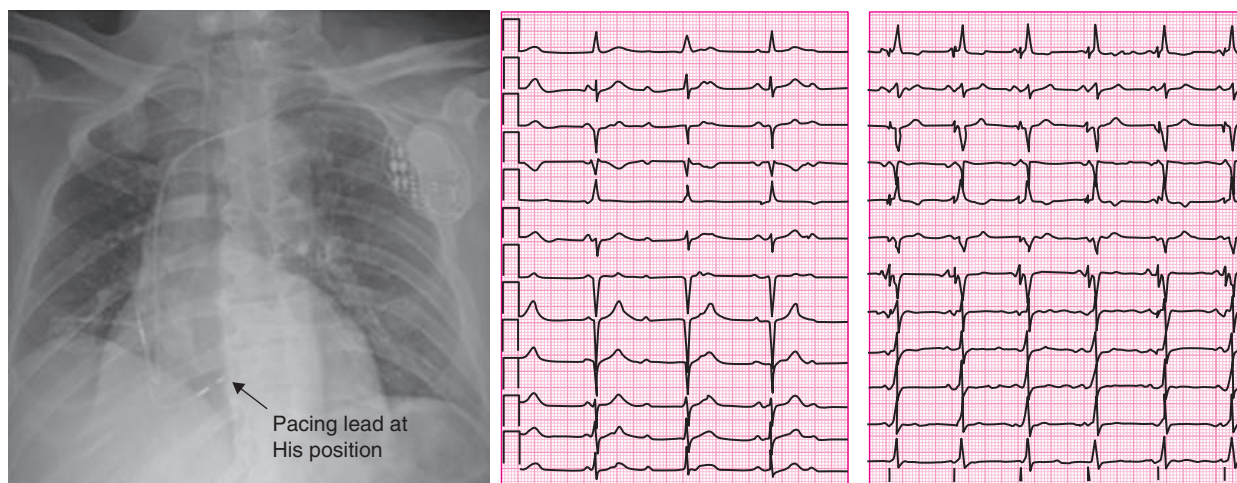


FIGURE 252-6 Left bundle branch area pacing. The chest radiograph on the left shows a dual-chamber pacemaker with a pacing lead in the right atrium (upper left) and a pacing lead in the region of proximal ventricular septum to achieve physiologic pacing by pacing deep enough in the septum to achieve left bundle branch area pacing. The electrocardiograms demonstrated intrinsic conduction with complete heart block on the left and atrial sensed, ventricular paced rhythm with a narrow QRS complex by capturing the specialized conduction system of the heart.

less well established, although AV synchrony in patients with sinus rhythm and AV block is typically desired.

Physiologic Ventricular Pacing In patients with left ventricular ejection fraction <50% and AV block who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time, techniques to provide more physiologic ventricular activation are preferred to right ventricular pacing to prevent heart failure. Cardiac resynchronization therapy (CRT) involves placement of an additional pacing lead in a lateral or anterolateral branch of the coronary sinus to allow for simultaneous right ventricle and lateral left ventricle pacing leading to a more physiologic left ventricular contraction. CRT pacing has been shown to improve outcomes and mortality in appropriately selected patients. Physiologic ventricular pacing has also been achieved with placement of a ventricular pacing lead in the region of the His bundle. His bundle pacing recruits the specialized conduction system, leading to a more physiologic cardiac contraction. In addition to His bundle pacing, left bundle branch area pacing in the proximal interventricular septal region has also been shown to achieve a more physiologic pacing response. The selection of pacing lead location should be individualized based on expected pacing requirements, underlying heart disease, and level of conduction block (Fig. 252-6).

The availability of leadless miniaturized pacing systems may be appropriate in selected patients. Leadless pacemakers are completely self-contained devices that are implanted via the femoral vein into the right atrium and ventricle. The technology for these devices continues to evolve, and the most recent models are capable of detecting atrial mechanical contraction to allow for the preservation of AV synchrony. The device can provide single- or dual-chamber pacing in addition to containing technology that can sense atrial activity (utilizing the accelerometer in the pacemaker) to coordinate an atrial sensed, ventricular paced rhythm. Leadless pacemakers can be particularly useful in patients with vascular access limitations. Because there is no intravascular pacing wire or implanted subcutaneous pacemaker generator, the long-term infection rate is lower and there is no risk of lead fracture (Fig. 252-7).

Several studies have failed to demonstrate a difference in mortality rate in older patients with AV block treated with a single- (VVI) compared with a dual- (DDD) chamber pacing mode. In some of the studies that randomized pacing mode, the risk of chronic atrial fibrillation and stroke risk decreased with physiologic pacing. In patients with sinus rhythm and AV block, the very modest increase in risk with dual-chamber pacemaker implantation appears to be justified to avoid the possible complications of single-chamber pacing.

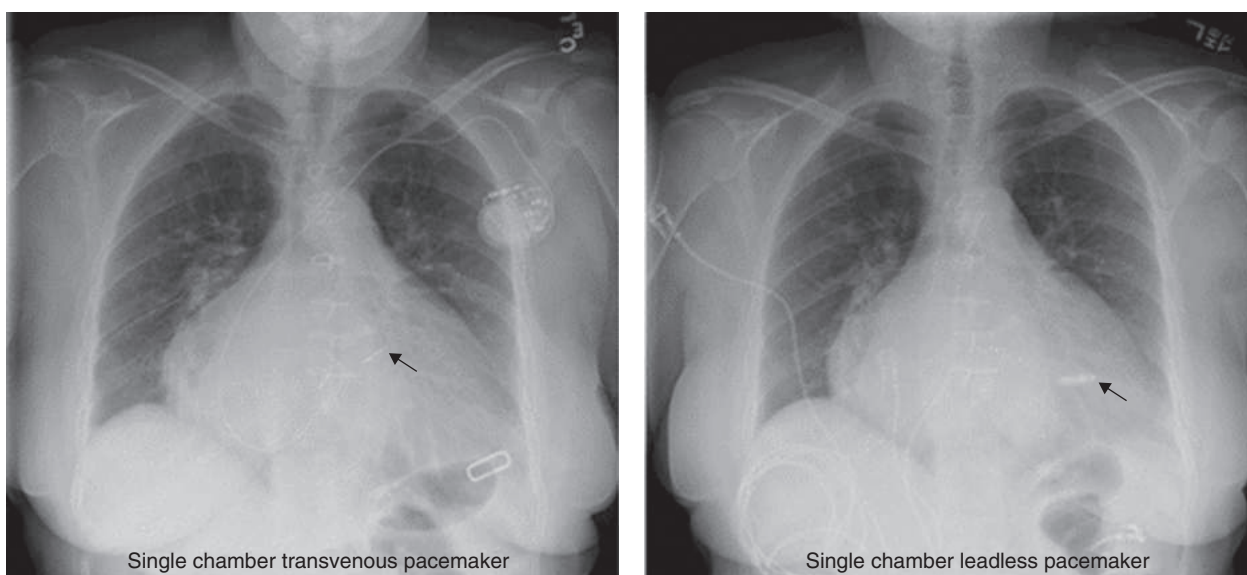


FIGURE 252-7 Types of pacemakers. A single-chamber pacemaker with the pacing lead in the right ventricular outflow tract (arrow) is shown on the left. A single-chamber leadless pacemaker (arrow) is shown on the right.

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- KUSUMOTO FM et al: 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 16:e128, 2019.
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253 Approach to Supraventricular Arrhythmias

William H. Sauer, Paul C. Zei

Supraventricular arrhythmias refer to all abnormal heart rhythms originating above the level of the ventricle including the atria and the atrioventricular (AV) junction. Supraventricular arrhythmias include premature atrial contractions (PACs), wandering atrial pacemaker, sinus arrhythmia, nonphysiologic sinus tachycardia, atrial tachycardia, junctional tachycardia, atrial flutter, and atrial fibrillation. Supraventricular arrhythmias that result in an elevated heart rate (>100 beats/min) are broadly defined as *supraventricular tachycardias* (SVTs). SVTs originate from or are dependent on conduction through the atrium or AV node to the ventricles. Most produce narrow QRS complex tachycardia (QRS duration <120 ms) characteristic of ventricular activation over the Purkinje system and, thus, are sometimes referred to as a narrow-complex tachycardias. The QRS morphology of the SVT is usually identical to the sinus rhythm QRS. Conduction block in the left or right bundle branch or activation of the ventricles from an accessory pathway produces a wide QRS complex during SVT that must be distinguished from ventricular tachycardia (VT). Mechanisms of supraventricular tachyarrhythmia can be divided into physiologic sinus tachycardia and pathologic tachycardia (**Table 253-1**).

Pathologic tachycardia can be further subclassified by mechanism as reentrant arrhythmias dependent on AV nodal conduction (e.g., AV nodal reentry tachycardia), large reentry circuits within the atrial tissue alone (e.g., atrial flutter), or focal atrial tachycardias that can be due to automaticity or small reentry circuits. The prognosis and treatment vary considerably depending on the mechanism and underlying heart disease. SVT can be of brief duration, termed *nonsustained*, or can be sustained such that an intervention, such as cardioversion, catheter ablation, or drug administration, is required for termination and maintenance of sinus rhythm. Episodes that occur with sudden onset and termination are referred to as paroxysmal. *Paroxysmal supraventricular tachycardia* (PSVT) refers to a family of tachycardias including AV node reentry, AV reciprocating tachycardia using an accessory pathway, and atrial tachycardia described in subsequent chapters (**Fig. 253-1**).

Other supraventricular arrhythmias that may or may not be symptomatic include PACs, sinus arrhythmia, ectopic atrial rhythm, and accelerated junctional rhythm. Atrial flutter and atrial fibrillation may present as a tachycardia or may be adequately rate controlled with or without AV nodal blocking agents; these entities are discussed separately (**see Chaps. 255, 256, 257, and 258**).

CLINICAL PRESENTATION

Symptoms of supraventricular arrhythmia vary depending on the rate, duration, associated heart disease, and comorbidities and include palpitations, chest pain, dyspnea, diminished exertional capacity, and

TABLE 253-1 Mechanisms of Supraventricular Arrhythmias

Physiologic Sinus Tachycardia

Defining feature: normal sinus mechanism precipitated by exertion, stress, exogenous or endogenous stimulants, concurrent illness

Pathologic Supraventricular Tachycardia (SVT)

A. Tachycardias originating from the atrium

Defining feature: tachycardia may continue despite beats that fail to conduct to the ventricles, indicating that the atrioventricular (AV) node is not participating in the tachycardia circuit

1. Inappropriate sinus tachycardia

Defining feature: tachycardia from the normal sinus node area that occurs without an identifiable precipitating factor as a result of dysfunctional autonomic regulation

2. Focal atrial tachycardia (AT)

Defining feature: regular atrial tachycardia with defined P wave; may be sustained, nonsustained, paroxysmal, or incessant; frequent sites of origin occur along the valve annuli of left or right atrium, pulmonary veins, coronary sinus musculature, superior vena cava

3. Atrial flutter and macroreentrant atrial tachycardia

Defining feature: macroreentry reflected as organized atrial activity on an electrocardiogram (ECG), commonly seen as sawtooth flutter waves at rates typically faster than 200 beats/min

4. Atrial fibrillation

Defining feature: chaotic rapid atrial electrical activity with variable ventricular rate; the most common sustained cardiac arrhythmia in older adults

5. Multifocal atrial tachycardia

Defining feature: multiple discrete P waves often seen in patients with pulmonary disease during acute exacerbations of pulmonary insufficiency

B. AV nodal reentry tachycardia (AVNRT)

Defining feature: paroxysmal regular tachycardia with P waves visible at the end of the QRS complex or not visible at all; the most common paroxysmal sustained tachycardia in healthy young adults; more common in women

C. Tachycardias associated with accessory atrioventricular pathways

1. Orthodromic AV reciprocating tachycardia (AVRT)

Defining feature: paroxysmal sustained tachycardia similar to AV nodal reentry; during sinus rhythm, evidence of ventricular preexcitation may be present (Wolff-Parkinson-White syndrome) or absent (concealed accessory pathway)

2. Preexcited tachycardia

Defining feature: wide QRS tachycardia with QRS morphology similar to ventricular tachycardia

- Antidromic AV reciprocating tachycardia—regular paroxysmal tachycardia
- Atrial fibrillation with preexcitation—irregular wide-complex or intermittently wide-complex tachycardia, some with dangerously rapid rates faster than 250/min
- Atrial tachycardia or flutter with preexcitation

Other Supraventricular Arrhythmias

A. Premature atrial contractions (PACs)

Defining feature: sinus rhythm with an early atrial complex distinct from the sinus P wave resulting in an irregular rhythm. A pattern of ectopy (i.e., trigeminy, bigeminy) is sometimes seen with PACs

B. Sinus arrhythmia

Defining feature: irregular rhythm with a sinus P wave and with P-P intervals varying with respiration

C. Accelerated junctional rhythm

Defining feature: paroxysmal regular rhythm with P waves visible at the end of the QRS complex or not visible at all

D. Ectopic atrial rhythm

Defining feature: regular rhythm with a rate <100 beats/min but usually faster than sinus rhythm and with a P wave distinct from sinus that may or may not sustain

occasionally syncope. Rarely, a supraventricular arrhythmia precipitates cardiac arrest in patients with Wolff-Parkinson-White (WPW) syndrome or severe heart disease, such as hypertrophic cardiomyopathy. Asymptomatic supraventricular arrhythmias are often captured on routine electrocardiographic (ECG) recordings and sometimes prompt

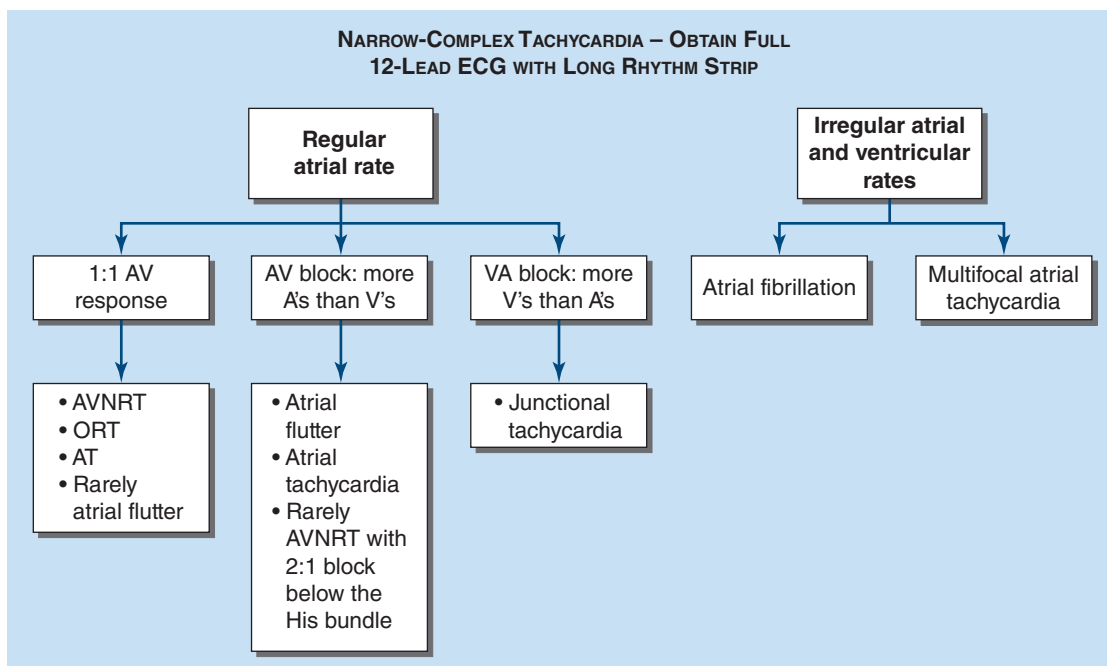


FIGURE 253-1 Diagnostic possibilities based on the appearance of the 12-lead electrocardiogram (ECG) recorded during an episode of supraventricular tachycardia (SVT). AT, focal atrial tachycardia; AVNRT, atrioventricular (AV) nodal reentry tachycardia; ORT, orthodromic AV reentry tachycardia.

referral to a cardiologist. Most asymptomatic supraventricular arrhythmias do not require treatment or further evaluation.

INITIAL EVALUATION

The diagnosis of SVT is most often entertained when evaluating a patient for arrhythmia-related symptoms or when evidence of ventricular preexcitation is seen on an ECG as an outpatient. Diagnosis of SVT requires obtaining an ECG at the time of symptoms ([Fig. 253-2](#)). Ventricular preexcitation on the resting ECG suggests AV reciprocating tachycardia using an accessory pathway. When the arrhythmia is ongoing at the time of recording, the ECG usually establishes or suggests the diagnosis. In the urgent care or inpatient setting, treatment of SVT will often involve vagal maneuvers or carotid sinus massage (CSM) to achieve AV block ([Table 253-2](#)). In the appropriate patient, CSM should be used cautiously, if at all, if there is concern for carotid atherosclerosis that may be embolized during manipulation. If this is unsuccessful, the administration of 6 or 12 mg of adenosine to cause transient AV block is usually successful in terminating an AV nodal-dependent SVT or diagnosing a non-AV nodal-dependent SVT such as atrial tachycardia or atrial flutter. There are some atrial tachycardias

that are adenosine sensitive, and thus, termination of an SVT with adenosine does not exclude this potential diagnosis.

For transient arrhythmias, ambulatory ECG recording is warranted. Patients will often have access to ECG recording devices, such as a watch or smartphone-enabled ECG recording electrode pair. Therefore, a patient may have an ECG diagnosis before seeing a physician ([Fig. 253-3](#)).

Exercise testing is useful for assessing exercise-related symptoms and potentially evoking the arrhythmia. Additional evaluation for underlying cardiac disease and to exclude potentially dangerous arrhythmias should be performed based on the clinical scenario. Occasionally, an invasive electrophysiology study is warranted to provoke the arrhythmia with pacing, confirm the mechanism, and risk stratify the patient, but most commonly, this is performed at the time of intended catheter ablation to treat the arrhythmia.

Paroxysmal SVT is most commonly encountered in patients who do not have structural heart disease. Other supraventricular arrhythmias, particularly atrial fibrillation, are often associated with a variety of heart diseases. At initial evaluation, history and examination should assess possible underlying heart disease. Any abnormal findings may warrant further cardiac evaluation.

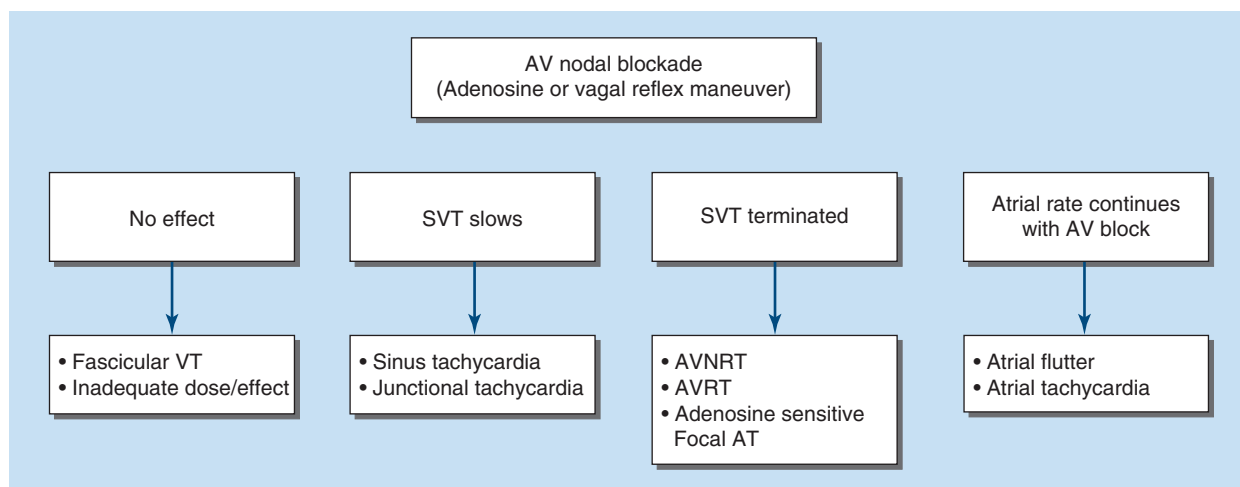
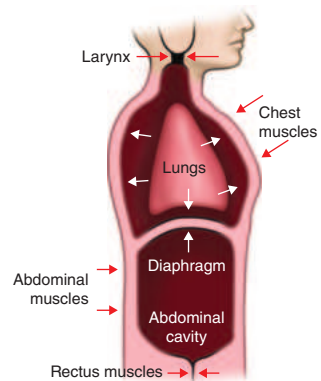
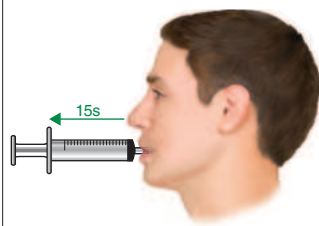


FIGURE 253-2 Diagnostic effect of increasing atrioventricular (AV) node blockade with vagal maneuvers, carotid sinus massage, adenosine, verapamil, or beta blockers. AT, focal atrial tachycardia; AVNRT, atrioventricular nodal reentry tachycardia; AVRT, atrioventricular reciprocating tachycardia; SVT, supraventricular tachycardia.



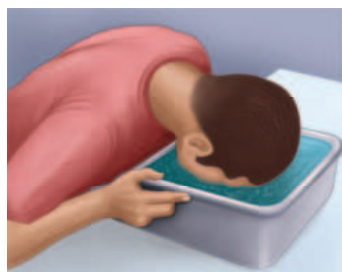
Holding breath while bearing down to increase intrathoracic pressure



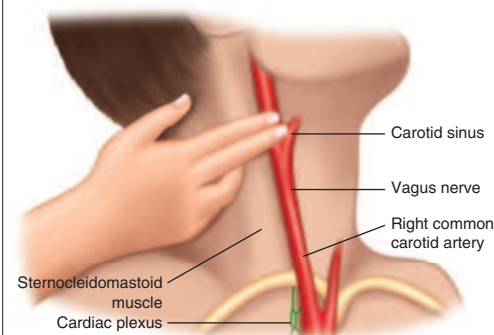
Breathing hard into a syringe against pressure to increase intrathoracic pressure



Raise legs abruptly to increase venous return



Submerge face into cold water (diver's reflex)



Carotid sinus massage



Adenosine

Heart Rate Over 120 —♥ 200 BPM

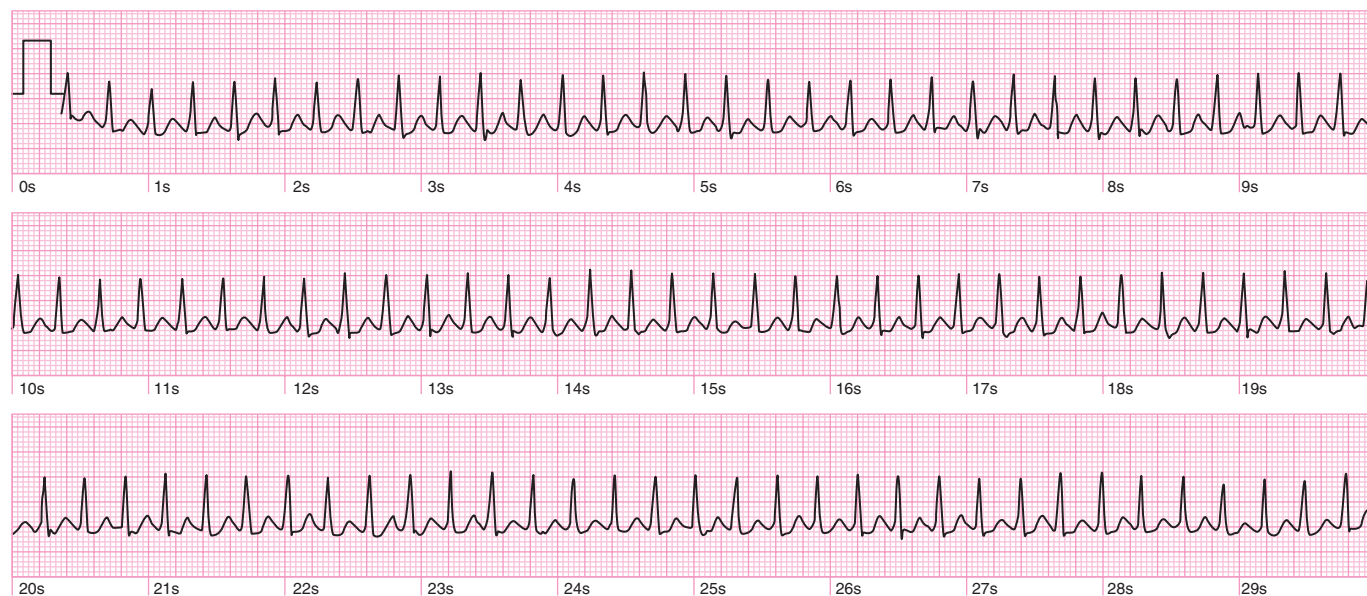
Average

This ECG was not checked for AFib because your heart rate was over 120 BPM.

If you repeatedly get this result or you're not feeling well, you should talk to your doctor.

Reported Symptoms

- Rapid pounding, or fluttering heartbeat
- Chest tightness or pain
- Fainting



25 mm/s, 10 mm/mV, Lead I, 511Hz, iOS 12.1.4, watchOS 5.1.3, Watch4,2 — The waveform is similar to a Lead I ECG. For more information, see Instructions for Use.

FIGURE 253-3 Narrow-complex tachycardia recorded by a consumer wearable monitor (Apple watch). Afib, atrial fibrillation; ECG, electrocardiogram.

The most common SVT is sinus tachycardia in response to physiologic stress, such as exercise, but it can also be a manifestation of acute illness. The first step in diagnosis of SVT is to consider the possibility of sinus tachycardia. Therapy is then determined by the clinical findings and probable diagnosis. If sinus tachycardia is diagnosed, treatment of the underlying inciting cause is the primary approach. If the arrhythmia is ongoing and is not due to sinus tachycardia, initial assessment determines whether immediate therapy is needed to terminate the arrhythmia or slow the rate. Arrhythmias that cause hypotension, impaired consciousness, angina, or heart failure warrant immediate therapy, guided by the type of arrhythmia. Treatment options for specific types of SVT are discussed in more detail in subsequent chapters and include pharmacologic and procedural interventions.

FURTHER READING

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known as the crista terminalis where the posterior smooth atrial wall derived from the sinus venosus meets the trabeculated anterior portion of the right atrium. Patients with sinus tachycardia will often seek medical attention with the uncomfortable awareness of their heartbeat as their chief complaint. Often, an arrhythmia is suspected because of the similar constellation of symptoms that accompanies supraventricular and ventricular tachycardia or atrial and ventricular ectopy. However, a careful review of the 12-lead electrocardiogram (ECG) reveals a characteristic P wave originating from the superior and lateral aspect of the right atrium with a positive deflection in leads I, II, and III and a biphasic morphology in lead V_1 . Sinus P waves are characterized by a frontal plane axis directed inferiorly and leftward, with positive P waves in leads II, III, and aVF; a negative P wave in aVR; and an initially positive biphasic P wave in V_1 . Normal sinus rhythm has a range of rates between 60 and 100 beats/min (Fig. 254-1).

SINUS ARRHYTHMIA

Sinus arrhythmia is a common finding that is usually asymptomatic and related to normal physiology in healthy individuals. The rhythm is defined as arising from a sinus node origin but with irregularity between P-P intervals of >120 ms. When there is an irregularity in the heart rhythm and there are different P-wave morphologies observed, then this arrhythmia is most likely due to premature atrial contractions (PACs) and not sinus arrhythmia. Sinus arrhythmia usually occurs at rest and is often eliminated with higher rates observed with exertion due to removal of vagal tone. The three types of sinus arrhythmias observed are respirophasic, ventriculophasic, and nonphasic. Respirophasic sinus arrhythmia occurs when vagal tone is inhibited reflexively during inspiration and is restored with expiration. A similar phenomenon is seen with breath-holding leading to exaggerated pauses most often seen with obstructive sleep apnea. Ventriculophasic sinus arrhythmia is most often observed with heart block or after a premature ventricular contraction (PVC). The P-P interval is shortened when there is an interposed ventricular complex seen in these conditions possibly related to the triggered baroreceptor reflex from the subsequent beat after a longer ventricular filling time and increased stroke volume. Nonphasic sinus arrhythmia refers to variations in sinus P-P intervals unrelated to the cardiac or respiratory cycle. Regardless of the mechanism, asymptomatic sinus arrhythmia does not warrant further cardiac evaluation and is not considered pathogenic.

254 Physiologic and Nonphysiologic Sinus Rhythm

William H. Sauer, Paul C. Zei

The sinus node is composed of a group of cells located in the lateral superior aspect of the junction between the right atrium and superior vena cava, within the superior aspect of the thick ridge of muscle

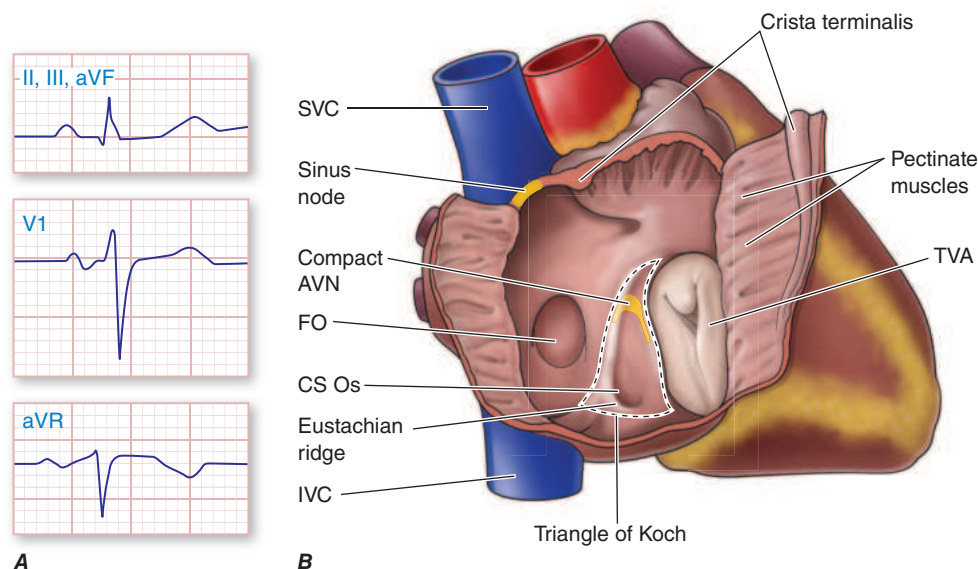


FIGURE 254-1 Right atrial anatomy pertinent to normal sinus rhythm and supraventricular tachycardia. **A**, Typical P-wave morphology during normal sinus rhythm based on standard 12-lead electrocardiogram. There is a positive P wave in leads II, III, and aVF and a biphasic, initially positive P wave in aVR. **B**, Right atrial anatomy seen from a right lateral perspective with lateral wall opened to view the septum. AVN, atrioventricular node; CS Os, coronary sinus ostium; FO, fossa ovalis; IVC, inferior vena cava; TVA, tricuspid valve annulus.

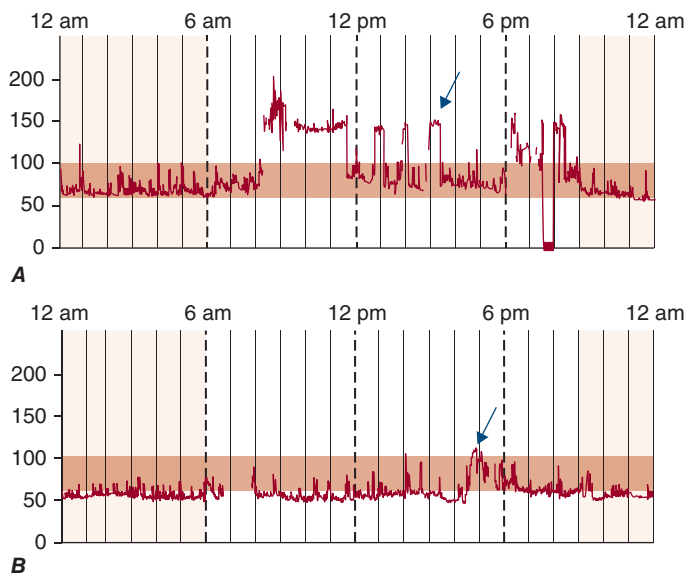


FIGURE 254-2 Outpatient telemetry monitor in a patient with intermittent atrial tachycardia (**A**) and normal physiologic sinus tachycardia (**B**).

PHYSIOLOGIC SINUS TACHYCARDIA

Sinus tachycardia (>100 beats/min) typically occurs in response to sympathetic stimulation and/or vagal withdrawal, whereby the rate of spontaneous depolarization of the sinus node increases and the focus of earliest activation within the node typically shifts more leftward and closer to the superior septal aspect of the crista terminalis, thus producing taller P waves in the inferior limb leads when compared to normal sinus rhythm. Sinus bradycardia is defined as rates <60 beats/min; however, bradycardia can be normal during sleep and in fit individuals.

Sinus tachycardia is considered physiologic when it is an appropriate response to exercise, stress, or illness. Sinus tachycardia can be difficult to distinguish from focal atrial tachycardia (see below) that originates near the sinus node. A causative factor (e.g., exertion) and a gradual rate increase favor a diagnosis of sinus tachycardia, whereas abrupt tachycardia onset and offset favor atrial tachycardia (Fig. 254-2).

The distinction can be difficult and occasionally requires extended ECG monitoring or invasive electrophysiology study. Treatment for physiologic sinus tachycardia is aimed at the underlying condition, but frequently, no therapy is necessary. Consideration to abnormal thyroid conditions and anemia should be given in patients with sinus tachycardia as these represent reversible causes. In addition, structural and functional cardiovascular abnormalities can present as sinus tachycardia, especially pulmonary embolism, and thus must be ruled out in the appropriate clinical scenario before considering sinus tachycardia as nonphysiologic. Finally, as sinus rate varies widely between individuals, a relatively elevated sinus rate (whether at rest or during exercise) without underlying cause, particularly without symptoms, typically does not warrant treatment (Table 254-1).

TABLE 254-1 Common Causes of Sinus Tachycardia

Physiologic Causes

Emotion, physical exercise, sexual intercourse, pain, pregnancy

Pathologic Causes

Anxiety, panic attack, anemia, fever, dehydration, infection, malignancies, hyperthyroidism, hypoglycemia, pheochromocytoma, Cushing's disease, diabetes mellitus with evidence of autonomic dysfunction, pulmonary embolus, myocardial infarction, pericarditis, valve disease, decompensated heart failure, shock, alcohol withdrawal

Drugs

Epinephrine, norepinephrine, dopamine, dobutamine, atropine, β_2 -adrenergic receptor agonists (salbutamol), methylxanthines, doxorubicin, daunorubicin, beta blocker withdrawal, caffeine, alcohol

Illicit Drugs

Amphetamines, cocaine, lysergic acid diethylamide, psilocybin, ecstasy, cocaine

NONPHYSIOLOGIC SINUS TACHYCARDIA

Inappropriate sinus tachycardia is an uncommon condition in which the sinus rate increases spontaneously at rest or out of proportion to physiologic stress or exertion and is within a spectrum of ill-defined conditions associated with autonomic dysregulation. The underlying mechanism remains elusive, but it may be related to imbalance between sympathetic and parasympathetic inputs to the sinus node, altered membrane automaticity of sinus node cells, or a combination of both. Affected individuals are often women in the third or fourth decade of life. Fatigue, dizziness, and even syncope may accompany palpitations, which can be disabling. Additional symptoms of chest pain, headaches, and gastrointestinal upset are common. Inappropriate sinus tachycardia must be distinguished from appropriate sinus tachycardia and from focal atrial tachycardia arising from a region near the sinus node. The distinction between physiologic sinus tachycardia due to an anxiety disorder and inappropriate sinus tachycardia can be difficult. Therapy is often ineffective or poorly tolerated. Careful titration of beta blockers may reduce symptoms. Clonidine and serotonin reuptake inhibitors have also been used. Ivabradine, a drug that blocks the I_f current that causes spontaneous sinus node depolarization, is approved in the United States for use in heart failure but has also been effective in the treatment of inappropriate sinus tachycardia. Catheter ablation of the sinus node to modify and thereby decrease the sinus rate has been performed, but long-term control of symptoms is usually poor and can result in a permanent pacemaker requirement due to resultant symptomatic sinus bradycardia or arrest, or chronotropic incompetence (Fig. 254-3).

Postural orthostatic tachycardia syndrome (POTS) is characterized by symptomatic sinus tachycardia that occurs with postural change from a supine position to standing. The sinus rate increases by 30 beats/min or to >120 beats/min within 10 min of standing and in the absence of hypotension. Symptoms are often similar to those in patients with inappropriate sinus tachycardia. POTS is sometimes due to autonomic dysfunction following a viral illness and may resolve spontaneously over 3–12 months. Prolonged postviral symptoms after COVID-19 infection, sometimes referred to as “long COVID,” have been ascribed to autonomic dysfunction and a POTS-like presentation. Volume expansion with salt supplementation, oral fludrocortisone, compression stockings, and the α -agonist midodrine, often in combination, can be helpful. Exercise training has also been shown to improve symptoms

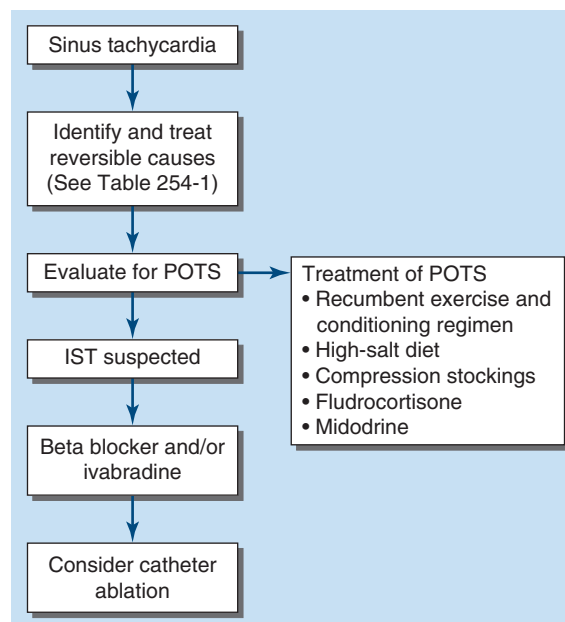


FIGURE 254-3 Evaluation and treatment of sinus tachycardia. For the patient who presents with sinus tachycardia, reversible causes of appropriate sinus tachycardia must be excluded and treated as indicated. Otherwise, evaluation for a spectrum of syndromes resulting in inappropriate sinus tachycardia should be undertaken. Potential directed therapies are shown. IST, inappropriate sinus tachycardia; POTS, postural orthostatic tachycardia syndrome.

and should be a part of a treatment strategy to reduce symptoms. While it is sometimes difficult to differentiate inappropriate sinus tachycardia from POTS, recognition of these distinct clinical syndromes is critical for treatment. Sinus node modification will be ineffective for the treatment of POTS and will possibly exacerbate the nontachycardia components of the condition. Likewise, treatment strategies aimed at increasing blood pressure will not be appropriate for inappropriate sinus tachycardia.

FURTHER READING

MAYUGA KA et al: Sinus tachycardia: A multidisciplinary expert focused review. *Circ Arrhythm Electrophysiol* 15:e007960, 2022.

VERNINO S et al: Postural orthostatic tachycardia syndrome (POTS): State of the science and clinical care from a 2019 National Institutes of Health Expert Consensus Meeting-Part 1. *Auton Neurosci* 235:102828, 2021.

255 Focal Atrial Tachycardia

William H. Sauer, Paul C. Zei

The underlying mechanisms of focal atrial tachycardia (AT) include abnormal automaticity, triggered automaticity, or a small reentry circuit in diseased atrial tissue. The term *focal* is used to differentiate this form of AT from typical and atypical atrial flutter but does not define a mechanism of the arrhythmia. ATs can originate from most regions of the atria, including atrial tissue extending into a pulmonary vein, the coronary sinus, or vena cava. It can be sustained, nonsustained, paroxysmal, or incessant. Focal AT accounts for ~10% of paroxysmal supraventricular tachycardia (PSVTs) in patients referred for catheter ablation. Nonsustained focal AT is commonly observed on ambulatory electrocardiogram (ECG) recordings, and the prevalence increases with age. Asymptomatic nonsustained ATs are often labeled as “SVT” on monitor reports, prompting patients to seek advice on catheter ablation. However, treatment is not recommended for asymptomatic nonsustained AT identified on ECG monitoring. Frequent atrial ectopy and nonsustained AT are often precursors to more significant arrhythmias such as atrial fibrillation and atrial flutter. Occasionally, nonsustained, frequent atrial ectopy or short bursts of AT may be symptomatic and require therapy similar to that required for focal AT (Fig. 255-1).

AT can occur in the absence of structural heart disease or may be associated with any condition that causes atrial fibrosis, including atrial tissue targeted with prior catheter ablation. Areas of fibrosis can act as a nidus for abnormal automaticity from injured but partially living cells or microreentry in zones of slow conduction within and on the border of fibrotic areas. Sympathetic stimulation is a promoting factor, and the emergence of AT can be a sign of underlying illness or drug toxicity. In particular, AT with atrioventricular (AV) block is characteristic of digitalis toxicity. Symptoms from AT are highly variable but similar to other supraventricular tachycardias (SVTs), and incessant AT can cause tachycardia-induced cardiomyopathy.

AT typically presents with 1:1 AV conduction or with AV block in a Wenckebach or fixed (e.g., 2:1 or 3:1) pattern. Because it is not dependent on AV nodal conduction, AT will not terminate with AV block, and the atrial rate will not be affected, which distinguishes AT from most AV nodal-dependent SVTs, such as AV nodal reentry and AV reentry using an accessory pathway (see below). A so-called warm-up phase when the atrial activation rate increases after initiation or a cool-down phase when the rate slows prior to termination also favors AT rather than AV nodal-dependent SVT, as this is a common observation with enhanced automaticity. P waves are often discrete, with an intervening isoelectric segment, in contrast to atrial flutter and macroreentrant AT because atrial activation from a focal source occurs through a small portion of the tachycardia cycle (Fig. 255-2).

When 1:1 conduction to the ventricles is present, the arrhythmia can resemble sinus tachycardia typically with a P-R interval shorter than the R-P interval, *particularly when sympathetic tone results in rapid AV nodal conduction*. It can be distinguished from sinus tachycardia by the P-wave morphology, which usually differs from sinus P waves depending on the location of the focus. Focal AT tends to originate in areas of complex atrial anatomy, such as the crista terminalis, valve annuli, atrial septum, and atrial muscle extending along cardiac thoracic veins (superior vena cava, coronary sinus, and pulmonary veins), and the location can often be approximated by the P-wave morphology. AT from the atrial septum will frequently have a narrower P-wave duration than sinus rhythm. AT from the left atrium will usually have a monophasic, positive P wave in lead V_1 and negative P waves in I and aVL, indicating an activation wavefront away from the left atrial free wall. AT that originates from superior atrial locations, such as the superior vena cava or superior pulmonary veins, will be positive in the inferior limb leads II, III, and aVF, whereas AT from a more inferior location, such as the ostium of the coronary sinus, will inscribe negative P waves in these same leads. When the focus is in the superior aspect of the crista terminalis, close to the sinus node, however, the P wave will resemble that of sinus tachycardia. Abrupt onset and offset then favor AT rather than sinus tachycardia. Depending on the atrial rate, the P wave may fall on top of the T wave, or during 2:1 conduction,

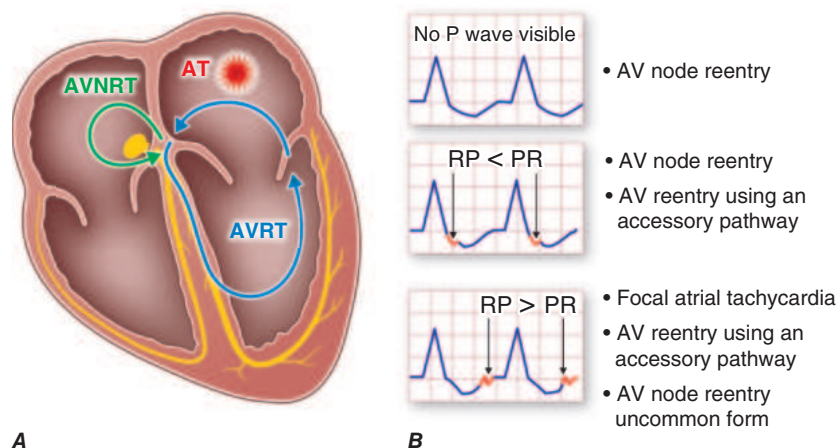


FIGURE 255-1 Common mechanisms underlying paroxysmal supraventricular tachycardia along with typical R-P relationships. **A.** Schematic showing a four-chamber view of the heart with atrioventricular (AV) node and specialized conduction tissue (His-Purkinje) in yellow. Atrial tachycardia (AT; red circuit) is confined completely to atrial tissue. Atrioventricular nodal reentry tachycardia (AVNRT; green circuit) uses AV nodal and perinodal atrial tissue. Atrioventricular reentry tachycardia (AVRT; blue circuit) uses atrial and ventricular tissue, accessory pathway between the ventricle and atrium, AV node, and His-Purkinje tissue as part of the reentry circuit. **B.** Typical relation of the P wave to QRS, commonly described as the R-P to P-R relationship, for the different tachycardia mechanisms.

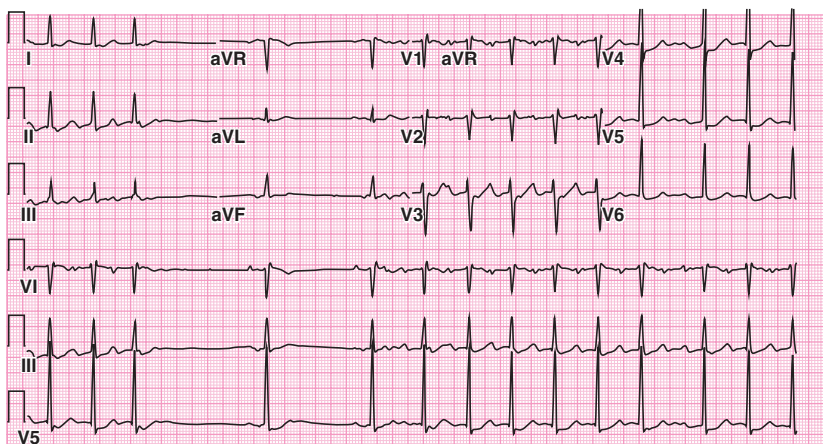
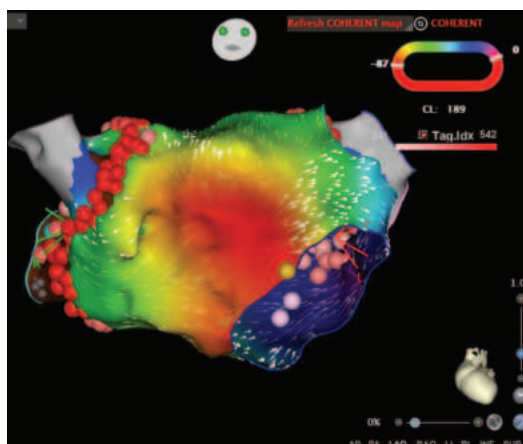


FIGURE 255-2 Focal atrial tachycardia. In the right panel, a surface 12-lead electrocardiogram shows focal intermittent atrial tachycardia. Note the discrete P waves, with isoelectric segments between, as well as the sinus rhythm. The left panel shows an electroanatomic map of the same focal atrial tachycardia originating from the anterior interatrial septum, as viewed in an anterior-posterior (AP) view of the left atrium obtained during electrophysiology study and ablation. The colors represent the timing of local electrical activation during each tachycardia atrial activation, showing a focal early (red) site. Additional markers of white “flects” represent conduction direction, demonstrating activation of the atrium dispersing from this focal site. Of note, the pink and red dots represent ablation lesions, in this case, for pulmonary vein isolation. (Adapted from J Brugada et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). *Eur Heart J* 41:655, 2020.)

every other P wave may fall coincident with the QRS. Maneuvers that increase AV block, such as carotid sinus massage, Valsalva maneuver, or administration of AV nodal-blocking agents, such as adenosine, are useful to create AV block that will expose the P wave.

Acute management of sudden-onset, sustained AT is the same as for other forms of PSVT, but the response to pharmacologic therapy is variable, likely depending on the mechanism (Fig. 255-3).

For AT due to reentry, administration of adenosine or vagal maneuvers may transiently increase AV block without terminating tachycardia. Some ATs terminate with a sufficient dose of adenosine, consistent with triggered activity as the mechanism. Cardioversion can be effective in some but fails in others because of immediate recurrence, suggesting automaticity as the mechanism in these cases. Beta blockers and calcium channel blockers may slow the ventricular rate by increasing AV block, which can improve tolerance of the arrhythmias, but large doses are sometimes required. Potential precipitating factors

and intercurrent illness should be sought and corrected. Underlying heart disease should be considered and excluded.

For patients with recurrent episodes, beta blockers, calcium channel blockers such as diltiazem or verapamil, and antiarrhythmic drugs such as flecainide, propafenone, disopyramide, sotalol, and amiodarone can be effective, but potential toxicities and adverse effects often warrant avoidance of long-term use.

Catheter ablation targeting the AT focus is effective in >80% of patients and is recommended for recurrent symptomatic AT when drugs fail or are not desired or for incessant AT causing tachycardia-induced cardiomyopathy. Although AT is often a precursor to atrial fibrillation or atrial flutter, the associated risk for stroke and, hence, indications for long-term anticoagulation are unclear but not considered equivalent.

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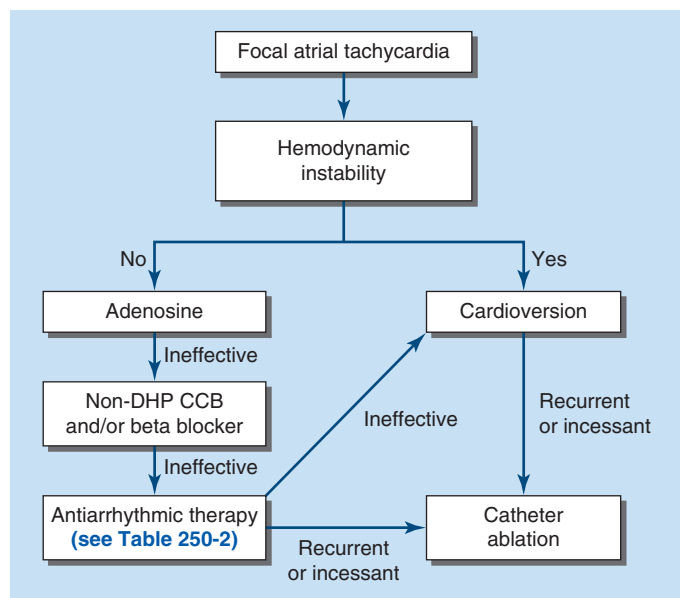


FIGURE 255-3 Clinical approach and treatment algorithm for management of focal atrial tachycardia. CCB, calcium channel blocker; DHP, dihydropyridine. (Adapted from J Brugada et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) [published correction appears in *Eur Heart J* 41:4258, 2020]. *Eur Heart J* 41:655, 2020.)

256

Paroxysmal Supraventricular Tachycardias

William H. Sauer, Paul C. Zei

In this chapter, sustained supraventricular tachycardias (SVTs) dependent on the atrioventricular (AV) node are discussed. These include AV nodal reentry tachycardia (AVNRT), junctional tachycardia, AV reciprocating tachycardia (AVRT) utilizing an accessory pathway, and a group of additional various SVTs that involve an accessory

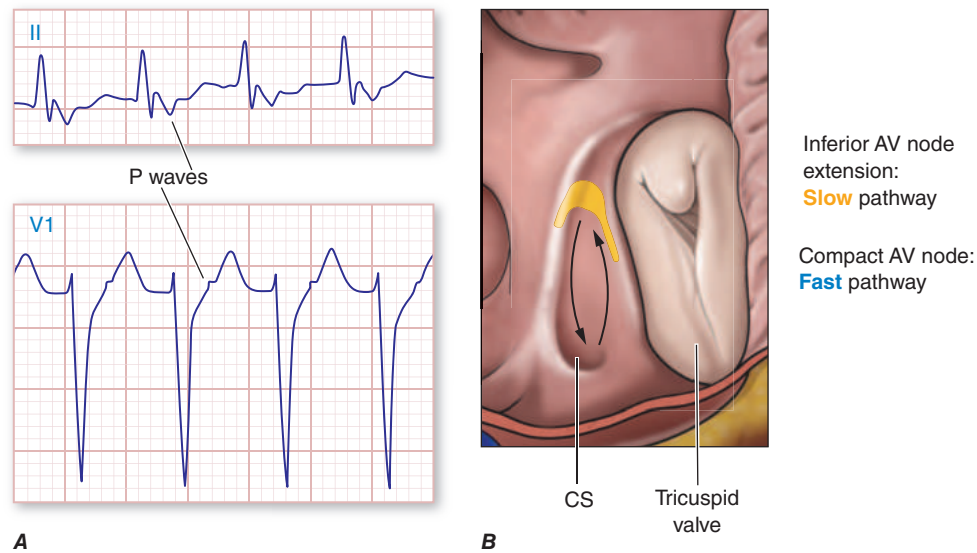


FIGURE 256-1 Atrioventricular (AV) node reentry. **A.** Leads II and V₁ are shown. P waves are visible at the end of the QRS complex and are negative in lead II and may give the impression of S waves in the inferior limb leads II, III, and aVF and an R' in lead V₁. **B.** Stylized version of the AV nodal reentry circuit within the triangle of Koch (see Fig. 254-1) that involves AV node and its extensions along with perinodal atrial tissue. CS, coronary sinus.

pathway, termed *preexcited tachycardias*. The term SVT encompasses a broad group of tachyarrhythmias based on anatomic origin and technically includes sinus tachycardia, atrial tachycardia (AT), atrial flutter, and atrial fibrillation; however, for the purposes of describing an organized approach to diagnosis and treatment of SVT, a separate discussion for these non-AV nodal-dependent SVTs are discussed elsewhere.

ATRIOVENTRICULAR NODAL REENTRY TACHYCARDIA

AVNRT is the most common form of paroxysmal supraventricular tachycardia (PSVT), representing ~60% of cases referred for catheter ablation. It most commonly manifests in the second to fourth decades of life, more often in women. It is usually well tolerated, but rapid tachycardia, particularly in the elderly, may cause angina, pulmonary edema, hypotension, or syncope. It is not usually associated with structural heart disease. In patients without associated heart disease, AVNRT is not a life-threatening arrhythmia; however, it may cause significant symptoms.

The mechanism is reentry involving the AV node and the perinodal atrium, made possible by the existence of multiple pathways for conduction from the atrium into the AV node that are capable of conduction in two directions (Fig. 256-1).

Most forms of AVNRT utilize a slowly conducting AV nodal pathway (right inferior extension) that extends from the compact AV node near the His bundle, inferiorly along the tricuspid valve annulus to the floor of the coronary sinus. The reentry wavefront propagates up this slowly conducting pathway to the compact AV node and then exits from the fast pathway at the top of the AV node. The path back to the

slow pathway probably involves the left atrial septum, which has connections to the coronary sinus musculature. More unusual forms of AVNRT utilize a left inferior extension that connects to the compact AV node through the roof of the coronary sinus or, in extremely rare cases, directly from the mitral valve annulus avoiding the coronary sinus musculature altogether. In typical forms, the conduction time from the compact AV node region to the atrium is similar to that from the compact node to the His bundle and ventricles, such that atrial activation occurs at about the same time as ventricular activation. The P wave is therefore inscribed during, slightly before, or slightly after the QRS and can be difficult to discern. Often the P wave is seen at the end of the QRS complex as a pseudo-r' in lead V₁ and pseudo-S waves in leads II, III, and aVF (Fig. 256-2).

More unusual forms of AVNRT have P waves falling later, anywhere between QRS complexes, in which case, an inverted P wave is seen in the inferior limb leads with the inverted P wave seen in the subsequent T wave. The rate can vary with sympathetic tone through its effect on the conduction time of AV nodal tissues. Simultaneous atrial and ventricular contraction results in atrial contraction against a closed tricuspid valve, producing a cannon A wave visible in the jugular venous pulse often perceived as a fluttering sensation in the neck. Elevated venous pressures may also lead to release of natriuretic peptides that cause post-tachycardia diuresis. In contrast to ATs, maneuvers or medications that produce AV nodal block terminate the arrhythmia. Acute treatment is the same as for other forms of PSVT (discussed below). Whether ongoing therapy is warranted depends on the severity of symptoms and frequency of episodes. Reassurance and instruction as to how to perform the Valsalva maneuver or other vagal

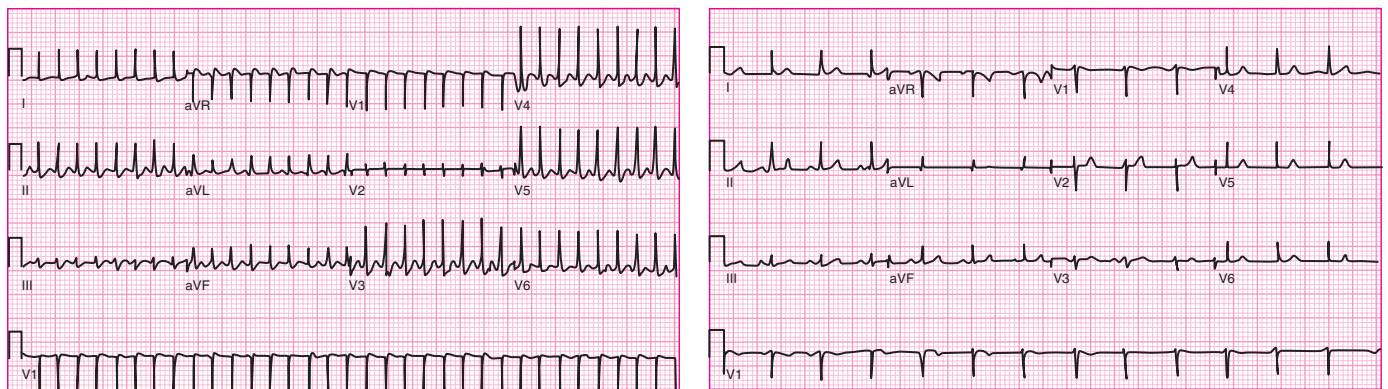


FIGURE 256-2 Atrioventricular nodal reentry tachycardia with retrograde P waves before and after adenosine termination.

nerve-stimulating maneuvers to terminate episodes are sufficient for many patients. Administration of an oral beta blocker, verapamil, or diltiazem at the onset of an episode can be used to facilitate termination. Chronic therapy with these medications or flecainide is an option if prophylactic therapy is needed. Catheter ablation of the slow AV nodal pathway is recommended for patients with recurrent or severe episodes or when drug therapy is ineffective, not tolerated, or not desired by the patient. Catheter ablation is curative in >95% of patients. The major risk is AV block requiring permanent pacemaker implantation, which occurs in <1% of patients.

JUNCTIONAL TACHYCARDIA

Junctional ectopic tachycardia (JET) is due to automaticity within the AV node. It is rare in adults and more frequently encountered as an incessant tachycardia in children, often in the perioperative period of surgery for congenital heart disease. It presents as a narrow QRS tachycardia, often with ventriculoatrial (VA) block, such that AV dissociation is present. JET can occur as a manifestation of increased adrenergic tone and may be seen after administration of isoproterenol, particularly after catheter ablation in the perinodal region. It may also occur for a short period of time after ablation for AVNRT. *Accelerated junctional rhythm* is a junctional automatic rhythm between 50 and 100 beats/min. Initiation may occur with gradual acceleration in rate, suggesting an automatic focus, or after a premature ventricular contraction, suggesting a focus of triggered automaticity. VA conduction is usually present, with P-wave morphology and timing such that it resembles AVNRT at a slow rate. It can be related to increased sympathetic tone and may produce palpitations. It usually does not require specific therapy.

ACCESSORY PATHWAYS AND THE WOLFF-PARKINSON-WHITE SYNDROME

Accessory pathways (APs) occur in 1 in 1500–2000 people and are associated with a variety of arrhythmias including narrow-complex PSVT, wide-complex tachycardias, and, rarely, sudden death. Most patients have structurally normal hearts, but APs are associated with Ebstein's anomaly of the tricuspid valve and forms of hypertrophic cardiomyopathy including *PRKAG2* mutations, Danon's disease, and Fabry's disease (Fig. 256-3).

APs are abnormal connections that allow conduction between the atrium and ventricles across the AV ring. They are present from birth and are due to failure of complete partitioning of atrium and ventricle by the fibrous AV rings. They occur across either an AV valve annulus or the septum, most frequently between the left atrium and free wall of the left ventricle, followed by posteroseptal, right free wall, and antero-septal locations. If the impulse from the sinus node conducts through the AP to the ventricle (antegrade) before the impulse conducts through the AV node and His bundle, then the ventricles are preexcited during sinus rhythm, and the electrocardiogram (ECG) shows a short P-R interval (<0.12 s), slurred initial portion of the QRS (delta wave), and prolonged QRS duration produced by slow conduction through direct activation of ventricular myocardium over the AP. The morphology of the QRS and delta wave is determined by the AP location and associated site of earliest ventricular activation, and the degree of fusion between the excitation wavefronts from conduction over the AV node and conduction over the AP (Fig. 256-4).

Right-sided pathways preexcite the right ventricle, producing a left bundle branch block–like configuration in lead V_1 , and often create marked preexcitation because of their relatively close proximity of the AP to the sinus node (Fig. 256-4). Left-sided pathways preexcite the left ventricle and may produce a right bundle branch–like configuration in lead V_1 and a negative delta wave in aVL, indicating initial depolarization of the lateral portion of the left ventricle that can mimic Q waves of lateral wall infarction (Fig. 256-4). Because of the relatively large distance between the sinus node and left free wall APs, preexcitation may be minimal or absent on 12-lead ECG. Preexcitation due to an AP at the diaphragmatic surface of the heart, typically in the paraseptal region, produces delta waves that are negative in leads III and aVF,

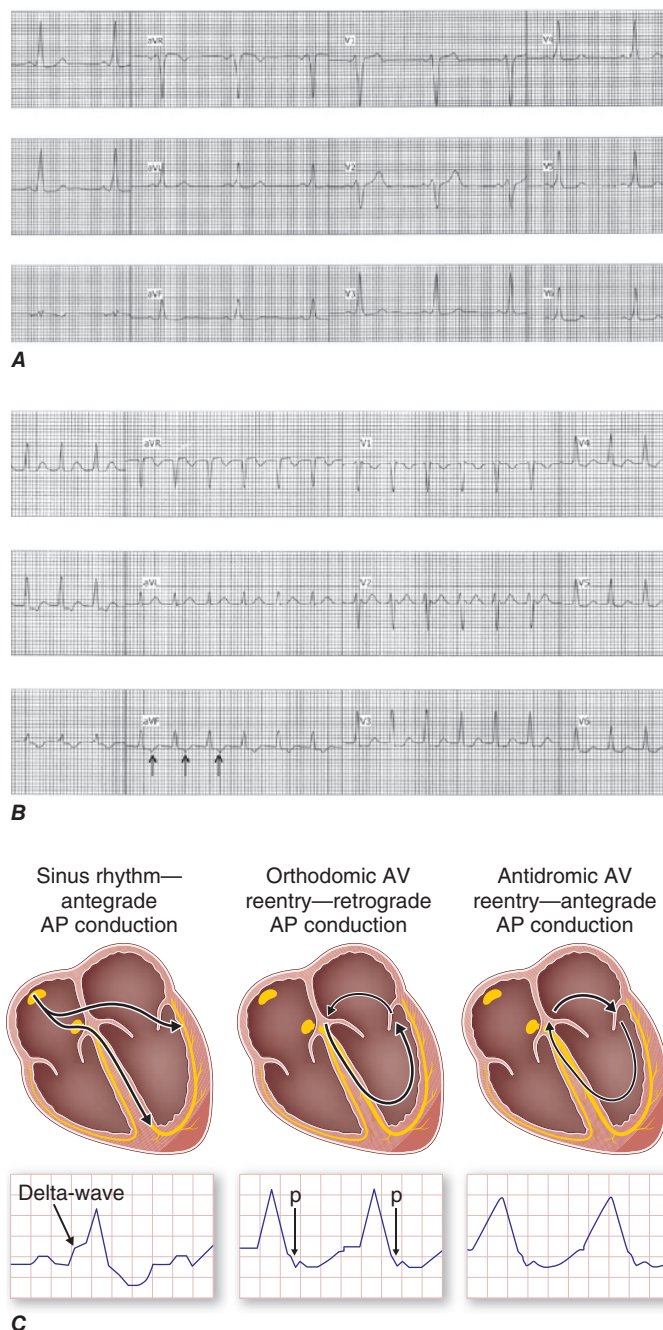


FIGURE 256-3 Wolff-Parkinson-White (WPW) syndrome. **A.** A 12-lead electrocardiogram in sinus rhythm (SR) of a patient with WPW demonstrating short P-R interval, delta waves, and widened QRS complex. This patient had an antero-septal location of the accessory pathway (AP). **B.** Orthodromic atrioventricular (AV) reentry in a patient with WPW syndrome using a posteroseptal AP. Note the P waves in the ST segment (arrows) seen in lead III and normal appearance of QRS complex. **C.** Three most common rhythms associated with WPW syndrome: sinus rhythm demonstrating antegrade conduction over the AP and AV node; orthodromic AV reentry tachycardia (AVRT) using retrograde conduction over the AP and antegrade conduction over the AV node; and antidromic AVRT using retrograde conduction over the AV node and antegrade conduction over the AP.

mimicking the Q waves of inferior wall infarction (Fig. 256-4). Preexcitation can be intermittent and disappear during exercise as conduction over the AV node accelerates and may take over ventricular activation completely.

Wolff-Parkinson-White (WPW) syndrome is defined as a preexcited QRS during sinus rhythm and episodes of PSVT. There are a number of variations of APs that may not cause preexcitation and/or arrhythmias. Concealed APs allow only retrograde conduction, from ventricle to atrium, so no preexcitation is present during sinus rhythm, but SVT

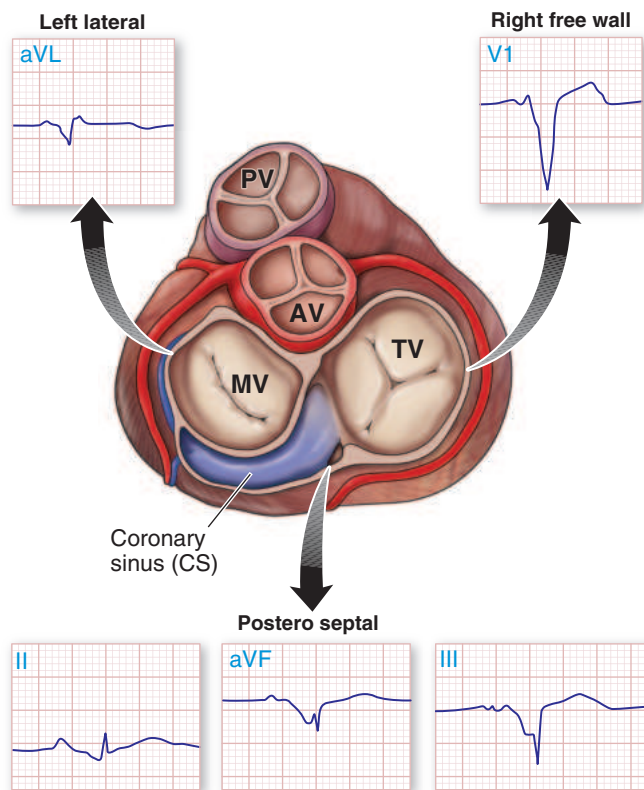


FIGURE 256-4 Potential locations for accessory pathways in patients with Wolff-Parkinson-White syndrome and typical QRS appearance of delta waves that can mimic underlying structural heart disease such as myocardial infarction of bundle branch block. AV, aortic valve; MV, mitral valve; PV, pulmonary valve; TV, tricuspid valve.

can occur. Other unusual forms of APs exist. Fasciculoventricular connections between the His bundle and ventricular septum produce preexcitation but do not cause arrhythmia, probably because the circuit is too short to promote reentry. Atriofascicular pathways, also known as Mahaim fibers, probably represent a duplicate AV node and His-Purkinje system that connect the right atrium to fascicles of the right bundle branch and produce a wide-complex tachycardia having a left bundle branch block configuration.

ATRIOVENTRICULAR RECIPROCATING TACHYCARDIA

The most common tachycardia caused by an AP is the PSVT designated *orthodromic AV reciprocating tachycardia*. The circulating reentry wavefront propagates from the atrium anterogradely over the AV node and His-Purkinje system to the ventricles and then reenters the atria via retrograde conduction over the AP. The QRS is narrow or may have typical right or left bundle branch block, but without preexcitation during tachycardia. Because excitation through the AV node and AP are necessary, AV or VA block results in tachycardia termination. During sinus rhythm, preexcitation is seen if the pathway also allows anterograde conduction. Most commonly, during tachycardia, the R-P interval is shorter than the P-R interval and can resemble AVNRT. Unlike typical AVNRT, P waves always follow the QRS and are never simultaneous with a narrow QRS complex because the ventricles must be activated before the reentry wavefront reaches the AP and conducts back to the atrium. The morphology of the P wave during tachycardia is determined by the pathway location, but it can be difficult to assess because it is usually inscribed during the ST segment. The P wave in posteroseptal APs is negative in leads II, III, and aVF, similar to that in AV nodal reentry, but P-wave morphology will differ from AV nodal reentry for pathways in other locations. Occasionally, an AP conducts extremely slowly in the retrograde direction, resulting in tachycardia with a long R-P interval, similar to most ATs. These pathways are

usually located in the septal region and have negative P waves in leads II, III, and aVF. Slow AP conduction facilitates reentry, often leading to nearly incessant tachycardia, known as *permanent junctional reciprocating tachycardia* (PJRT). Tachycardia-induced cardiomyopathy can occur. Without an invasive electrophysiology study, it may be difficult to distinguish this form of orthodromic AV reentry from atypical AV nodal reentry or AT.

PREEXCITED TACHYCARDIAS

Preexcited tachycardia occurs when the ventricles are activated by antegrade conduction over the AP. The most common mechanism is *antidromic AV reciprocating tachycardia* in which activation propagates from atrium to ventricle via the AP and then conducts retrogradely to the atria via the His-Purkinje system and the AV node (or rarely a second AP). The wide QRS complex is produced entirely via ventricular activation over the AP because there is no contribution of ventricular activation over more rapidly conducting specialized His-Purkinje fibers. This tachycardia is often indistinguishable from monomorphic ventricular tachycardia. The presence of preexcitation in sinus rhythm suggests the diagnosis.

Preexcited tachycardia also occurs if an AP allows antegrade conduction to the ventricles during AT, atrial flutter, atrial fibrillation (AF), or AV nodal reentry, otherwise known as bystander AP conduction. AF and atrial flutter are potentially life-threatening if the AP allows very rapid repetitive conduction (Fig. 256-5).

Approximately 25% of APs causing preexcitation allow minimum R-to-R intervals of <250 ms during AF and are associated with a higher risk of inducing ventricular fibrillation and sudden death. Preexcited AF presents as a wide-complex, very irregular rhythm. During AF, the ventricular rate is determined by the conduction properties of the AP and AV node. The QRS complex can appear quite bizarre and change on a beat-to-beat basis due to the variability in the degree of fusion from activation over the AV node and AP, or all beats may be due to conduction over the AP. Ventricular activation from the Purkinje system may depolarize the ventricular aspect of the AP and prevent atrial wavefront conduction over the AP. Slowing AV nodal conduction without slowing AP conduction can thereby facilitate AP conduction and dangerously accelerate the ventricular rate. Administration of AV nodal-blocking agents, including oral or intravenous verapamil, diltiazem, beta blockers, intravenous adenosine, and intravenous amiodarone, is contraindicated during preexcited AF. Rapid preexcited tachycardia should be treated with electrical cardioversion or intravenous procainamide or ibutilide, which may terminate the arrhythmia or slow the ventricular rate.

MANAGEMENT OF PATIENTS WITH ACCESSORY PATHWAYS

Acute management of orthodromic AV reentry is discussed below for PSVT. Patients with WPW syndrome may have wide-complex tachycardia due to antidromic AV reentry, orthodromic AV with bundle branch block, or a preexcited tachycardia, and treatment depends on the underlying rhythm. Initial patient evaluation should include assessment for aggravating factors, including intercurrent illness and factors that increase sympathetic tone. Examination should focus on excluding underlying heart disease. An echocardiogram is reasonable to exclude Ebstein's anomaly, forms of hypertrophic cardiomyopathy that can be associated with APs, or tachycardia-mediated cardiomyopathy.

Patients with preexcitation who have symptoms of arrhythmia are at risk for developing AF and sudden death if they have an AP that allows rapid antegrade conduction. The risk of cardiac arrest is in the range of 2 per 1000 patients in adults but is likely greater in children. An invasive electrophysiology study is recommended to assess whether the pathway can support dangerously rapid heart rates if AF were to occur, and it is usually combined with potentially curative catheter ablation. Catheter ablation is warranted for recurrent arrhythmias when drugs are ineffective, not tolerated, or not desired by the patient. Efficacy is in the range of 95% depending on the location of the AP. Serious complications occur in <3% of patients but can include AV

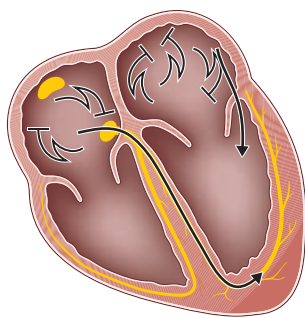


FIGURE 256-5 Preexcited atrial fibrillation (AF) due to conduction over a left free wall accessory pathway (AP). The electrocardiogram shows rapid irregular QRS complexes that represent fusion between conduction over the atrioventricular node and left free wall AP. Shortest R-R intervals between preexcited QRS complexes of <250 ms, as in this case, indicate a risk of sudden death with this arrhythmia.

block, cardiac tamponade, thromboembolism, coronary artery injury, and vascular access complications. The risk of AV block is higher when the AP is located near the AV node and/or His bundle, in the so-called anteroseptal or mid-septal locations. Procedure mortality is <1 in 1000 patients. Ambulatory monitoring or exercise testing is often used to gain reassurance that the AP is not high risk, evaluating for abrupt loss of conduction (preexcitation) at physiologic heart rates consistent with a low-risk pathway, but this is not completely reliable. Gradual loss of AP conduction with increased sympathetic tone does not reliably indicate low risk since this can occur as AV nodal conduction time shortens, and therefore, the possibility of rapid antegrade AP conduction is not excluded definitively.

For patients with concealed APs or known low-risk APs causing orthodromic AVRT, chronic therapy is guided by symptoms and frequency of events. Vagal maneuvers may terminate episodes, as may a dose of beta blocker, verapamil, or diltiazem taken at the onset of an episode. Chronic therapy with these agents or flecainide can reduce the frequency of episodes in some patients.

Adults who have preexcitation but no arrhythmia symptoms have a risk of sudden death estimated to be 1 per 1000 patient-years. Electrophysiology study is usually advised for people in occupations for which an arrhythmia occurrence would place them or others at risk, such as police, military, and pilots, or for individuals who desire evaluation for risk. Routine follow-up without therapy is reasonable in others. Children are at greater risk of sudden death, ~2 per 1000 patient-years.

TREATMENT

Paroxysmal Supraventricular Tachycardia

Acute management of narrow QRS PSVT is guided by the clinical presentation. Continuous ECG monitoring should be implemented, and a 12-lead ECG should always be obtained when possible, since this may be useful in determining the mechanism. In the presence of hypotension with unconsciousness or respiratory distress, QRS-synchronous direct current cardioversion is warranted, but this is rarely needed, because intravenous adenosine works promptly in most situations (see below). For stable individuals, initial therapy takes advantage of the fact that most PSVTs are dependent on AV nodal conduction (AV nodal reentry or orthodromic AV reentry) and, therefore, likely to respond to sympatholytic and vagotonic maneuvers and drugs. As these are administered, the ECG should be continuously recorded because the response can establish the diagnosis. AV block with only transient slowing of tachycardia may expose ongoing P waves, indicating AT or atrial flutter as the mechanism ([Fig. 256-6](#)).

Carotid sinus massage is reasonable provided the risk of carotid vascular disease is low, as indicated by absence of carotid bruits and no prior history of stroke. A Valsalva maneuver should be attempted in cooperative individuals, and if effective, the patient can be taught to perform this maneuver as needed. If vagal maneuvers fail or

257 Common Atrial Flutter and Macroreentrant and Multifocal Atrial Tachycardias

William H. Sauer, Jorge E. Romero, Paul C. Zei

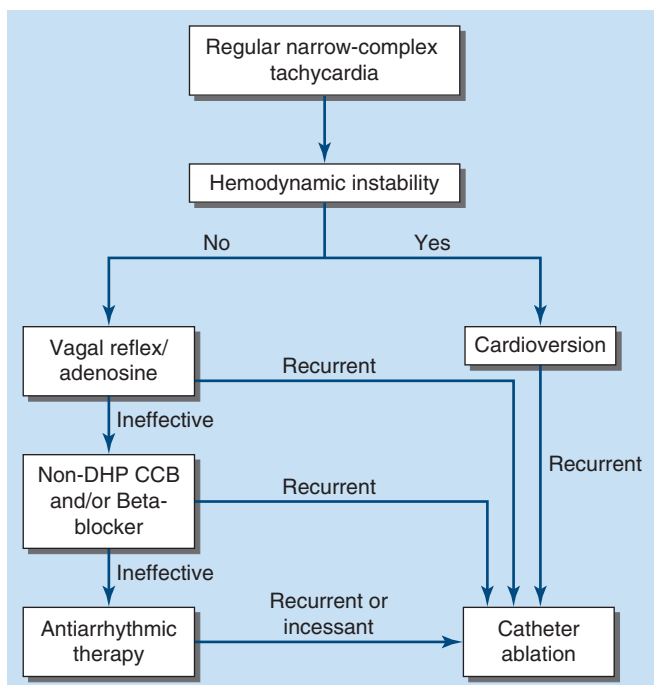


FIGURE 256-6 Treatment algorithm for patients presenting with hemodynamically stable paroxysmal supraventricular tachycardia. CCB, calcium channel blocker; DHP, dihydropyridine.

cannot be performed, intravenous adenosine will terminate the vast majority of PSVT episodes by transiently blocking conduction in the AV node. Adenosine may produce transient chest pain, dyspnea, and anxiety. It is contraindicated in patients with prior cardiac transplantation due to potential hypersensitivity due to surgical sympathetic denervation. It can theoretically aggravate bronchospasm. Adenosine precipitates AF, which is usually brief, in up to 15% of patients, so it should be used cautiously in patients with WPW syndrome in whom AF may produce hemodynamic instability. Intravenous beta blockers and calcium channel blockers (verapamil or diltiazem) are also effective but may cause hypotension before and after arrhythmia termination and have a longer duration of action. These agents can also be given orally and can be taken by the patient on an as-needed basis to slow ventricular rate and facilitate termination by Valsalva maneuver.

The differential diagnosis of wide-complex tachycardia includes ventricular tachycardia, PSVT with bundle branch block aberrancy, and preexcited tachycardia (see above). In general, these should be managed as ventricular tachycardia until proven otherwise. If the tachycardia is regular and the patient is stable, a trial of intravenous adenosine is reasonable. Very irregular wide-complex tachycardia is most likely preexcited AF or flutter (see above) and should be managed with cardioversion, intravenous procainamide, or ibutilide. If the diagnosis of PSVT with aberrancy is unequivocal, as may be the case in patients with prior episodes, treatment for PSVT with vagal maneuvers and adenosine is reasonable. In all cases, continuous ECG monitoring should be implemented, and emergency cardioversion and defibrillation should be available.

For management of PSVT outside of the acute setting, most patients with recurrent episodes are candidates for catheter ablation (see above).

FURTHER READING

BRUGADA J et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The task force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) Developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 41:655, 2020.

Macroreentrant atrial tachycardia is characterized by a large anatomic reentry circuit, often associated with areas of atrial scar tissue with slow conduction. *Common or typical right atrial flutter* is attributed to a wavefront of electrical propagation encircling the tricuspid valve annulus, bounded anteriorly by the annulus and posteriorly by the inferior vena cava and the Eustachian ridge. The wavefront passes between the inferior vena cava and the tricuspid valve annulus, known as the sub-Eustachian or cavotricuspid isthmus, where it is susceptible to interruption by catheter ablation. Thus, common atrial flutter is also known as *cavotricuspid isthmus-dependent atrial flutter*. This circuit most commonly revolves in a counterclockwise direction (as viewed looking toward the tricuspid annulus from the ventricular apex), which produces the characteristic negative sawtooth flutter waves in leads II, III, and aVF and positive P waves in lead V₁. When the direction is reversed, clockwise rotation produces the opposite P-wave vector in those leads and is called “reverse typical atrial flutter.” The atrial rate is typically 240–300 beats/min but may be slower in the presence of atrial disease or antiarrhythmic drugs. It often conducts to the ventricles with 2:1 atrioventricular (AV) block, creating a regular tachycardia at 140–150 beats/min, with flutter waves that may be difficult to discern from the T wave. Maneuvers that increase AV nodal block will typically expose flutter waves, allowing diagnosis. AV nodal disease or AV nodal-blocking agents may render the conduction ratio between atrium and ventricle higher, resulting in more obvious flutter waves (Fig. 257-1). However, controlling ventricular rates during atrial flutter with AV nodal-blocking agents is frequently challenging.

Common or typical right atrial flutter often occurs alongside atrial fibrillation and is frequently associated with atrial scarring from senescence or prior cardiac surgery. Nonetheless, the onset of typical atrial flutter has been proposed to be preceded by atrial fibrillation, indicating a potential transition from atrial fibrillation to atrial flutter due to a line of functional block or the coalescence of fibrillatory wavelets surrounding anatomic barriers such as the crista terminalis and eustachian valve. Interestingly, some patients with atrial fibrillation treated with antiarrhythmic drugs, particularly flecainide, propafenone, or amiodarone, may present with atrial flutter rather than atrial fibrillation, because these agents slow atrial conduction velocity and can promote reentry, in addition to suppressing ectopic atrial triggers. This mechanism highlights the complex interplay between atrial fibrillation and atrial flutter, as well as the influence of antiarrhythmic medications on arrhythmia presentation.

Macroreentrant atrial tachycardias (ATs) that are not dependent on conduction through the cavotricuspid isthmus are referred to as *atypical atrial flutters*, also known as “non-cavotricuspid isthmus-dependent” atrial flutters. They can occur in either atrium and are almost universally associated with areas of atrial scar. Right atrial atypical flutter often occurs after cardiac surgery if an atriotomy is performed in the right atrium as part of the surgery. Left atrial flutter and perimitral left

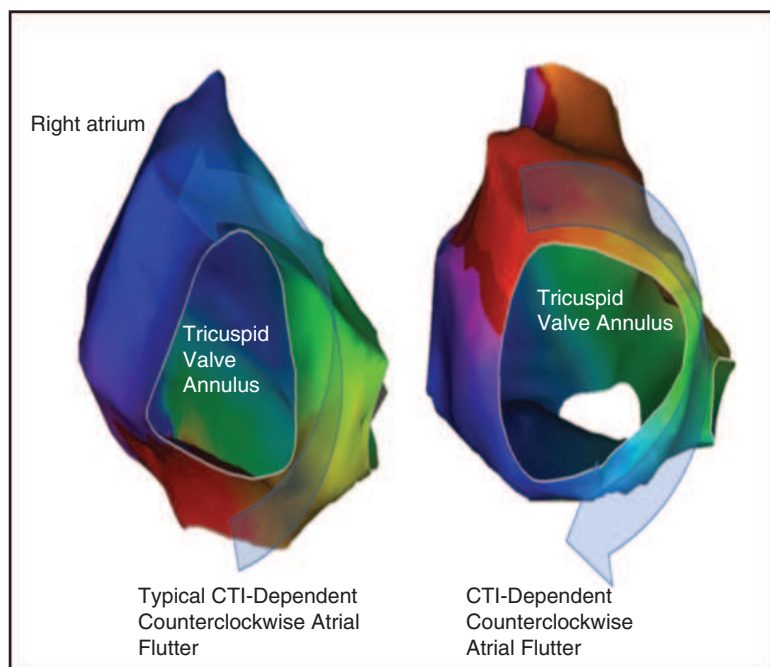
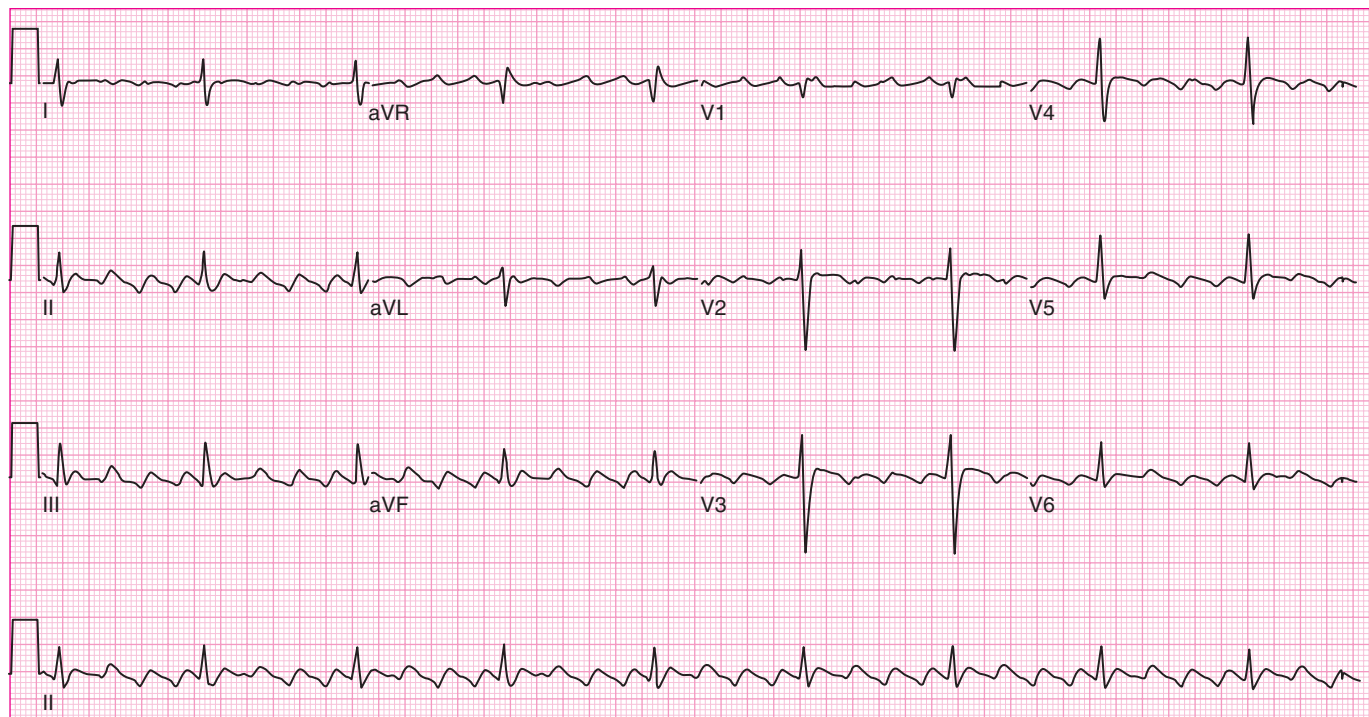


FIGURE 257-1 A 12-lead electrocardiogram (ECG) of typical or common atrial flutter (counterclockwise activation) is shown. Note the sawtooth pattern of atrial activation, with negative flutter (F) waves in inferior limb lead and positive flutter waves in lead V_1 , as well as 4:1 atrioventricular (AV) conduction during flutter. CTI, cavotricuspid isthmus.

atrial flutter are commonly seen after extensive left atrial ablation for atrial fibrillation or mitral valve surgery (Fig. 257-2). While the clinical presentation resembles common atrial flutter, it exhibits different P-wave morphologies. They can be difficult to distinguish from focal AT, and in most cases, the underlying mechanism can only be confirmed by an electrophysiology study (Fig. 257-3).

ATRIAL FLUTTER

Initial management of atrial flutter is similar to that for atrial fibrillation, discussed in more detail in Chap. 258. Anticoagulation therapy plays a pivotal role in preventing thromboembolic events in this population and should be determined based on individual thromboembolic risk profiles with the $\text{CHA}_2\text{DS}_2\text{-VASc}$ scoring system and bleeding risk assessment. Nonetheless, anticoagulation is crucial before considering

conversion to sinus rhythm, unless electrical cardioversion is warranted for hemodynamic instability or severe symptoms.

Rate control can be achieved with administration of AV nodal-blocking agents. However, achieving optimal rate control in atrial flutter may be more challenging compared to atrial fibrillation. Once rate control is achieved or the patient is hemodynamically stable, consideration is given to rhythm control strategies for restoring and maintaining sinus rhythm. Antiarrhythmic drug therapy such as sotalol, dofetilide, disopyramide, ibutilide, and amiodarone may be considered, but >70% of patients experience recurrences. Therefore, catheter ablation is recognized as first-line therapy due to its high success rate (i.e., >95%), low risk of complications, and low recurrence rates. However, up to half of the patients undergoing cavotricuspid isthmus ablation go on to develop atrial arrhythmias, with atrial fibrillation being the most

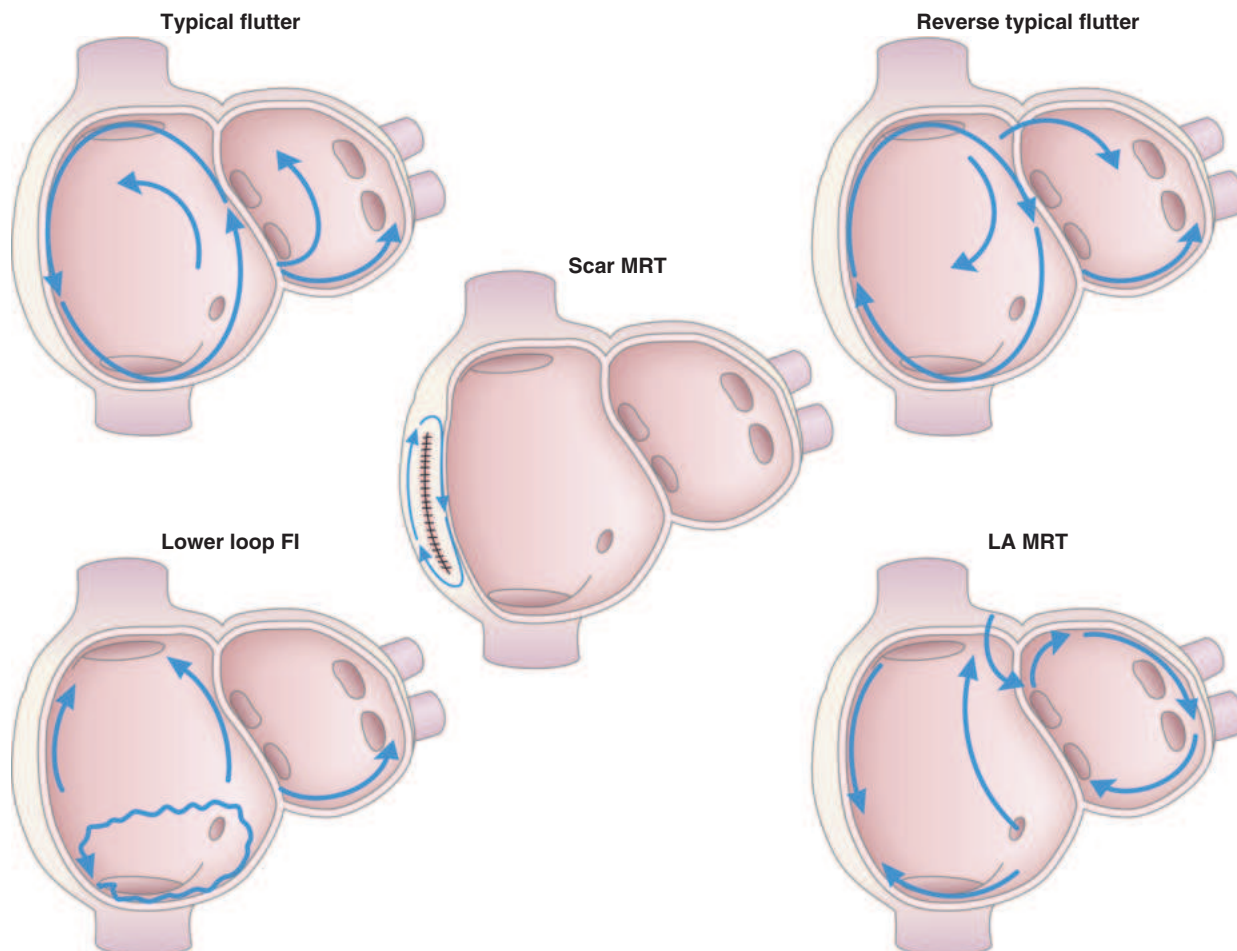


FIGURE 257-2 Types of atrial flutter and macroreentrant atrial tachycardia. The typical, reverse typical, and lower-loop flutter circuits all involve the low right atrial isthmus. Additionally, other forms of macroreentrant flutters encompass scar-mediated reentrant tachycardia and left atrial mitral isthmus flutter. FI, flutter; LA, left atrium; MRT, macroreentrant. (Reprinted with permission *Circulation*. 149:e1-e156, 2024. ©2023 American Heart Association, Inc.)

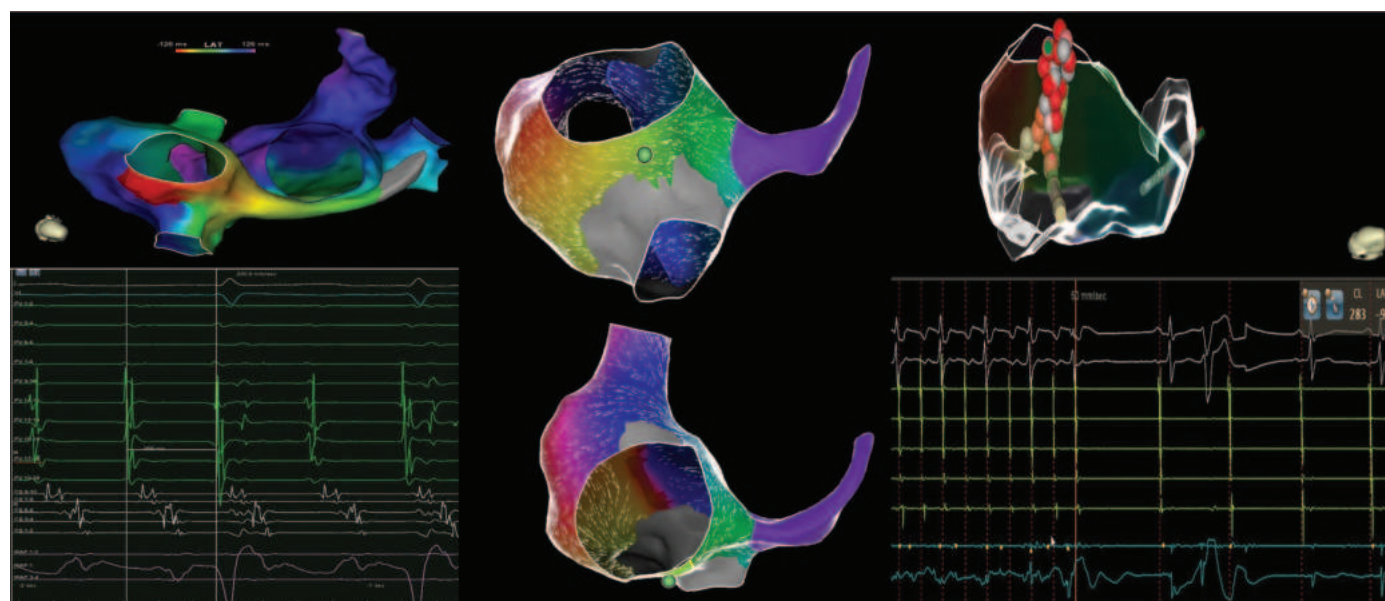


FIGURE 257-3 Electroanatomic mapping of typical atrial flutter. Electroanatomic maps reveal counterclockwise (more common) cavotricuspid isthmus (CTI)-dependent atrial flutter. These maps depict the electrical activation pattern during flutter, obtained during electrophysiologic study and catheter ablation. Colors refer to local activation time where “early meets late” (red-purple). In the *left panel*, electrograms display atrial flutter with a cycle length of 260 ms. The *middle panel* shows an activation map with vector integration, while the *right panel* illustrates termination of the atrial flutter into sinus rhythm by delivering radiofrequency ablation lesions in the CTI.

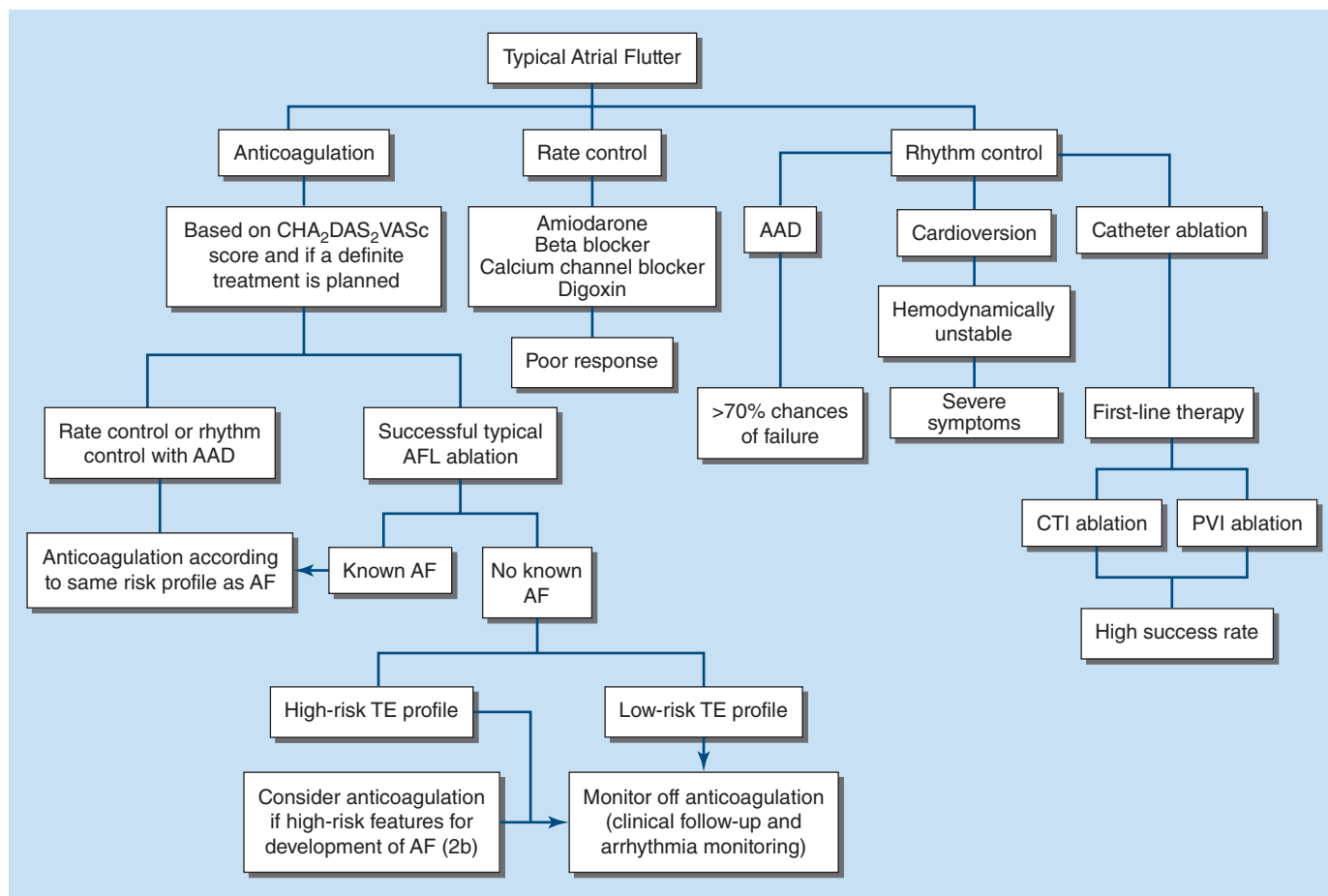


FIGURE 257-4 Approach to the patient with atrial flutter. AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; CTI, cavotricuspid isthmus; PVI, pulmonary vein isolation; TE, thromboembolic event. (Modified from JA Joglar et al: 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 149:e1, 2024.)

common among them. While prophylactic cavotricuspid isthmus ablation may not be beneficial in patients with atrial fibrillation, a recent study suggested that treating atrial flutter with pulmonary vein isolation as first-line therapy can prevent recurrent atrial flutter, in addition to reducing the risk of new-onset atrial fibrillation.

In summary, the management of atrial flutter involves a stepwise approach beginning with anticoagulation for thromboembolic prevention, followed by rate control to manage symptoms and hemodynamic stability and, more importantly, rhythm control to maintain sinus rhythm. Catheter ablation is increasingly favored as the first-line therapy for achieving long-term rhythm control and improving quality of life in these patients. More importantly, additional studies are needed to substantiate a more effective ablation strategy aimed at preventing the recurrence of atrial flutter and reducing the incidence of new-onset atrial fibrillation episodes. Lastly, postablation anticoagulation remains a subject of controversy, contingent upon the likelihood of developing atrial fibrillation (Fig. 257-4).

MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal AT (MAT) is characterized by a rhythm with at least three distinct P-wave morphologies, with rates typically from 100 to 150 beats/min. Unlike atrial fibrillation, MAT exhibits clear isoelectric intervals between P waves, and the atrial rate tends to be slower. The underlying mechanism is often attributed to triggered automaticity originating from multiple atrial foci. This condition is commonly observed in patients with chronic pulmonary disease and acute illnesses (Fig. 257-5).

Therapy for MAT is directed at treating the underlying disease and correcting any metabolic abnormalities. Electrical cardioversion is ineffective. Calcium channel blockers such as verapamil or diltiazem may be used to slow the atrial and ventricular rate. Patients with severe pulmonary disease often do not tolerate beta-blocker therapy well. MAT may respond to amiodarone, but long-term therapy with this agent is usually avoided due to its potential toxicities, particularly pulmonary fibrosis. The associated risk of thromboembolism in MAT remains unclear but is not considered to be the same as atrial fibrillation or atrial flutter.



FIGURE 257-5 Multifocal atrial tachycardia. Rhythm strip obtained from a patient with severe pulmonary disease during an acute illness. Note the irregularity of the rhythm but with distinct P waves. Arrows note three distinct P-wave morphologies.

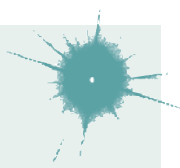
FURTHER READING

- BRUGADA J et al: 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The task force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC) developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 41:655, 2020.
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258

Atrial Fibrillation

William H. Sauer, Jorge E. Romero,
Paul C. Zei



PATHOPHYSIOLOGY AND EPIDEMIOLOGY

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by seemingly disorganized, rapid, and irregular atrial electrical activation, resulting in loss of organized atrial mechanical contraction. These rapid and irregular electrical signals input into the atrioventricular (AV) node, which determines ventricular activation and rate. The conducted ventricular rate is variable, resulting in an irregular, usually rapid ventricular rate, ranging typically between 110 and 160 beats/min in most. In some patients, the sustained ventricular rate can exceed 200 beats/min, whereas in others with either high vagal tone or AV nodal conduction disease, the ventricular rate may be excessively slow (Fig. 258-1).

The disorganized atrial activation is best appreciated in lead V_1 for this patient. AF is the most common sustained arrhythmia; as a result, it is a major public health issue. Prevalence increases with age, with >95% of AF patients >60 years of age. The prevalence in humans over age 80 is ~20%. The lifetime risk of developing AF for men aged 40 years old is ~25%. AF is slightly more common in men than women and more common in whites than blacks. Risk factors for developing AF in addition to age and underlying cardiac disease include hypertension, diabetes mellitus, cardiac disease, family history of AF, obesity, thyroid disease, and sleep-disordered breathing. AF is not a benign condition, with a 1.5- to 1.9-fold increased risk of mortality after controlling for underlying cardiac disease. Perhaps the most important consequence of AF is a significantly increased risk of stroke compared to the general population, causing ~25% of all strokes. AF has been detected up to 8.9% of patients within 6 months following cryptogenic stroke using insertable cardiac monitors.

The risk of dementia is increased in patients with AF, as is the risk of magnetic resonance imaging (MRI)-detected asymptomatic embolic infarct. AF, most often when ventricular rate remains uncontrolled for prolonged periods, increases the risk of developing congestive heart failure and cardiomyopathy. Moreover, as a corollary, patients with underlying heart disease, in particular cardiomyopathy and congestive heart failure, are at higher risk for developing AF. AF is a marker for worsened morbidity and mortality in patients with existing heart disease, although the precise extent of the independent risk increase associated with AF in heart disease is unclear. AF may, on occasion, be associated with an identifiable precipitating factor, such as hyperthyroidism, acute alcohol intoxication, myocardial infarction, pulmonary

embolism, pericarditis, and cardiac surgery, where AF occurs in up to 50% of patients postoperatively.

AF is clinically most typically defined by the pattern of episodes. Paroxysmal AF is defined as a pattern of AF episodes that occur and terminate with a relatively short duration either spontaneously or by pharmacologic or electrical cardioversion, most commonly defined as 7 days or less. Persistent AF refers to AF that occurs continuously for >7 days but <1 year, whereas long-standing persistent AF refers to AF that has been persistent for >1 year. These descriptors for AF correlate somewhat with the underlying pathophysiology of AF. AF tends to be a progressive condition, with, at this point, no definitive “cure” that will completely eliminate AF durably in a predictable fashion. The pathophysiology of AF, however, remains incompletely understood. Most data support a multifactorial process that leads to the development of manifest AF. Clinical and epidemiologic studies have demonstrated that, in addition to cardiovascular disease, age, alcohol use, obesity, hypertension, diabetes mellitus, and sleep-disordered breathing are associated with higher risk of developing AF. The proposed pathophysiology suggests a “final common pathway” of these risk factors leading to electrophysiologic changes in atrial tissues. Alterations in regulation of membrane channels and other proteins result in abnormal electrical excitability. Atrial tissues, in particular pulmonary vein musculature, exhibit enhanced automaticity, resulting in ectopic beats (premature atrial contractions), as shown in Fig. 258-2. Bouts of rapid atrial ectopy may then initiate either atrial tachycardia or frank AF. Additional cellular and, eventually, tissue remodeling results in abnormal conduction properties throughout the atria, including, in particular, shortening of atrial tissue refractory periods. This enables sustained AF through a combination of rapid automaticity-based “drivers” and areas of functional reentry. Further remodeling leads to the development of fibrosis and left atrial enlargement (Table 258-1).

These functional and anatomic changes in atrial tissues appear to correlate with the progression of clinical AF. AF tends to be a progressive disease in most, although exceptions occur. Typically, for a period of time, patients experience sporadic ectopic beats and short runs of atrial tachycardia, likely originating from the pulmonary veins, preceding the onset of frank AF.

Other regions of the atria have been demonstrated to produce ectopic depolarizations that may trigger AF; these include the posterior wall of the left atrium and muscular tissue sleeves within the superior vena cava, coronary sinus, or the remnant of the vein of Marshall. When enough frequent bursts of ectopic beats/tachycardia and/or changes in underlying substrate support the maintenance of AF for short periods, the patient develops episodes of paroxysmal AF. In the untreated patient, over time, as the electrical, contractile, and structural remodeling continues to progress, episodes of paroxysmal AF may be prolonged to the point of not terminating spontaneously, the hallmark of persistent AF. After further remodeling, not only do patients continue to long-standing persistent AF but also the efficacy of therapeutic interventions to restore sinus rhythm diminishes.

CLINICAL PRESENTATION AND MANIFESTATIONS

The clinical manifestations of AF result from (1) symptoms related to the irregular, often rapid but sometimes slow ventricular rates that result; (2) the hemodynamic consequences of altered cardiac function; (3) the consequences of cardioembolic phenomena; and/or (4) the impact of AF on cardiovascular function over time. AF is diagnosed by electrocardiogram (ECG), either by 12-lead standard ECG, limited lead ambulatory monitor ECG and implantable loop recorders, with findings of lack of organized atrial activity (no P wave), with an irregular ventricular response. The role of screening populations for AF is evolving with the use of wearable monitors and home ECG capabilities.

With irregular, rapid ventricular rates, there is variable cardiac displacement and contraction, resulting in the sensation of palpitations and awareness of the heartbeat, when of course, in a normal rhythm, most humans do not sense each heartbeat. Interestingly, many patients are, for the most part, unaware of the irregular ventricular beating for unknown reasons.

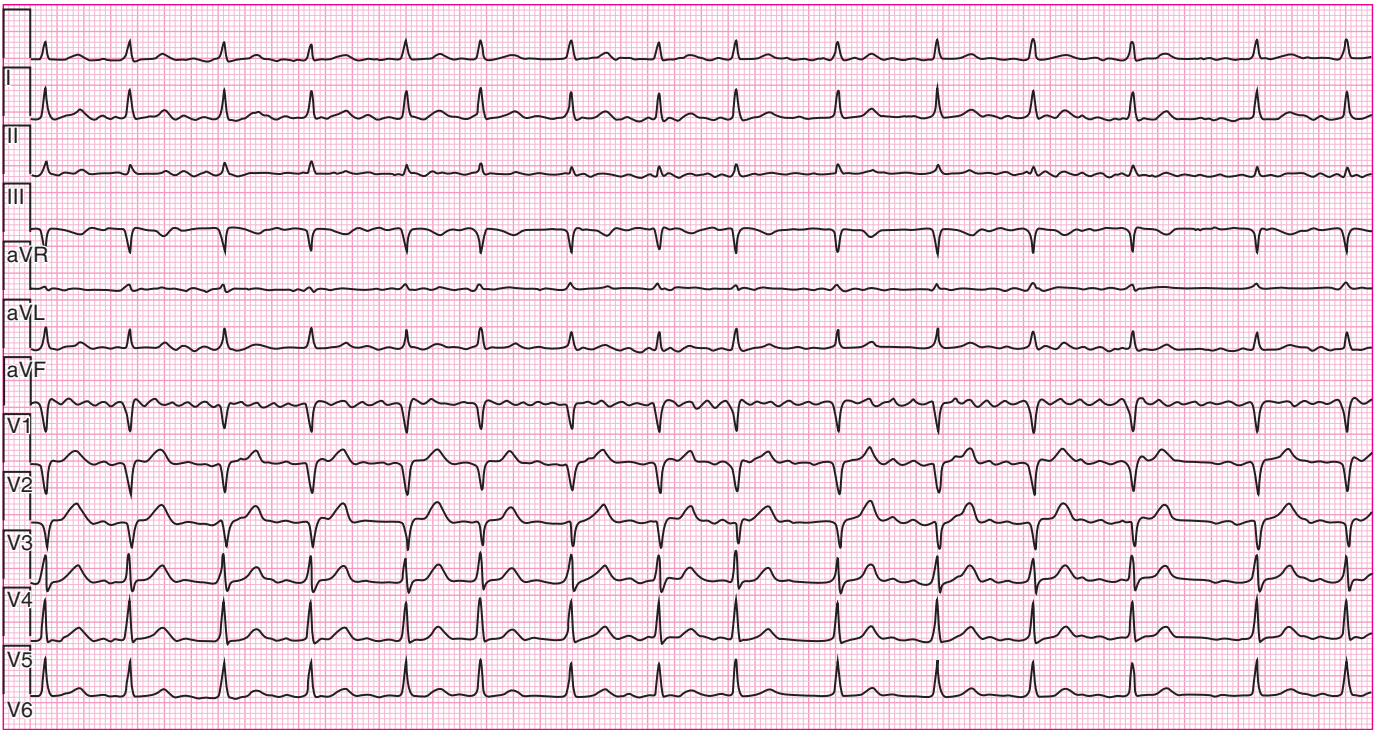


FIGURE 258-1 Electrocardiogram of an irregularly irregular heart rhythm without discernable P waves. The disorganized atrial activation is best appreciated in lead V₁ for this patient.

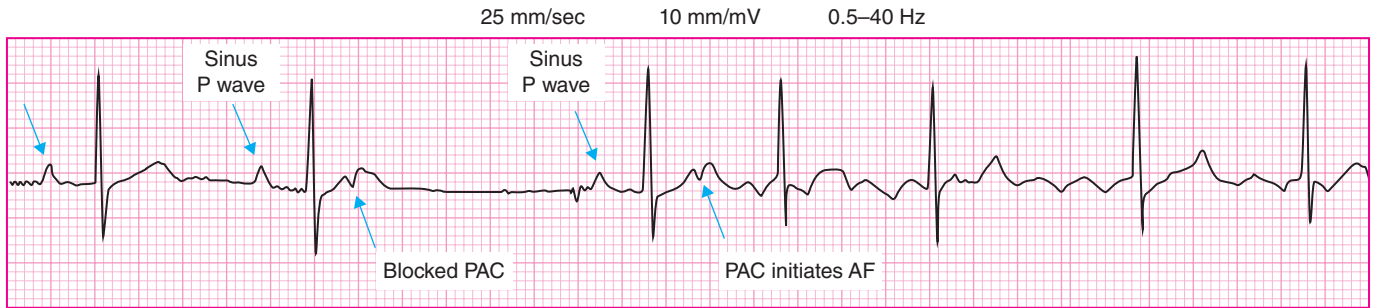
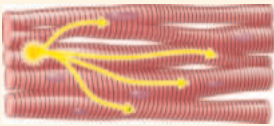
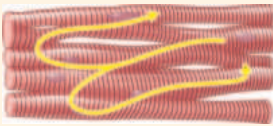


FIGURE 258-2 Surface electrocardiogram (ECG) of atrial ectopy initiating atrial fibrillation (AF). In this single-lead surface ECG recording, the tracing begins with two conducted sinus beats. A nonconducted premature atrial contraction (PAC) (labeled “blocked PAC”) is shown after the second QRS complex. After the next sinus P wave and QRS, an ectopic beat (PAC) initiates atrial fibrillation, as demonstrated by (somewhat organized) erratic atrial activity and an irregular ventricular response.

TABLE 258-1 Categorization of Atrial Fibrillation (AF) by Clinical Temporal Characteristics and Associated Features			
			
	PAROXYSMAL AF	PERSISTENT AF	LONG-STANDING PERSISTENT AF
Definition	Episodes self-terminate or via pharmacologic or electrical CV in <7 days	Episodes lasting >7 days and <1 year	Persistent AF >1 year
LA size	Normal to mildly enlarged	Mild to severely enlarged	Typically, severely enlarged
LA scar burden	Low	Moderate	High
Efficacy of AAD	Often effective	Not as effective	Usually refractory
When to offer ablation?	First-line therapy reasonable	First-line appropriate but usually offered after AAD failure	After AAD failure, not always a good option
Ablation technique	PV isolation alone usually effective	PV isolation and any identified non-PV AF source	PV isolation; additional ablation for substrate modification likely needed

Note: With paroxysmal, persistent, and long-standing persistent AF, definitions are based on duration of events and diagnosis overall. These categorizations correlate with LA size, LA scar burden, and resultant efficacy of medical and ablative therapies.
Abbreviations: AAD, antiarrhythmic drugs; CV, cardioversion; LA, left atrium; PV, pulmonary vein.

During AF, there is loss of the contribution of atrial systole to overall cardiac output and, with irregular ventricular rates, variable ventricular filling and, consequently, variable stroke volume. The resultant impact on overall cardiac output may result in exercise intolerance, fatigue, weakness, presyncope, or dyspnea. In patients with underlying cardiac disease, the additional hemodynamic compromise resulting from AF may result in exacerbation of the disease and/or heart failure symptoms. Patients with hypertrophic cardiomyopathy, coronary artery disease, valvular disease, heart failure with either depressed or preserved ejection fraction, or amyloidosis are particularly susceptible. In patients with concomitant AV nodal conduction disease, bradycardia during AF may result in presyncope or syncope. Pauses at the time of spontaneous conversion from AF to sinus rhythm, a manifestation of sinus node dysfunction that commonly occurs in patients with AF, may result in presyncope or syncope as well.

With the loss of atrial mechanical contraction, blood stasis may promote *in situ* thrombosis, which, when embolized, may result in a range of clinical consequences, most importantly, ischemic stroke. Thrombus formation occurs primarily in the left atrial appendage. Over time, recurrent thromboembolism to the brain, even if asymptomatic, may result in debilitating neurologic sequelae, including cognitive impairment. An increased risk of dementia in patients with AF may be the consequence of this phenomenon, although the contribution of chronic hypoperfusion in patients with long-standing persistent atrial fibrillation is unclear.

In patients with prolonged periods of rapid ventricular rates resulting from AF, there is risk of developing a tachycardia-induced cardiomyopathy, with associated depressed left ventricular function. Tachycardia-induced myopathy appears generally to be reversible once ventricular rates are controlled. In patients with long-standing persistent AF, the atria, especially the left atrium, tend to be more dilated and to contain a higher burden of fibrotic, noncontractile atrial tissue. The hemodynamic consequences of a noncompliant, fibrotic left atrium, including elevated left atrial filling pressures, volume overload, and congestive heart failure, have been described as “stiff left atrial syndrome.”

TREATMENT

Atrial Fibrillation

The treatment and management of the patient with AF centers on three aims: (1) control of patient symptoms through a strategy of rate control and/or rhythm control; (2) appropriate mitigation of thromboembolism risk; and (3) addressing modifiable risk factors for progression of AF. In the acute onset of AF, if significant hemodynamic compromise, pulmonary edema, or evidence of coronary ischemia is present, emergent cardioversion is recommended. Electrical cardioversion can be achieved with a QRS synchronous shock, preferably in a sedated patient, or via pharmacologic cardioversion, most typically with the intravenous administration of the class III antiarrhythmic ibutilide. Ibutilide should be avoided in patients with baseline prolonged QT interval or severe left ventricular dysfunction, given the risk of torsades des pointes. In the hemodynamically stable patient with new-onset AF, therapy should focus on control of ventricular rate to prevent hemodynamic sequelae, consideration of anticoagulation to mitigate thromboembolic risk, and consideration of restoration and maintenance of sinus rhythm—a so-called rhythm control strategy. If restoration of sinus rhythm is being considered, a more immediate risk of thromboembolism must be factored into the management strategy. Although there is a lack of definitive data, it is presumed that if the presenting episode of AF is >48 h or if the episode duration is unknown, there is risk for precipitating a thromboembolic complication through cardioversion, whether electrically or pharmacologically achieved. Therefore, in this circumstance, the patient should be either initiated on anticoagulation, with cardioversion deferred for at least 3 weeks after uninterrupted anticoagulation, or evaluated to exclude the presence of left atrial appendage thrombus. Most commonly,

transesophageal echocardiography (TEE) is used to evaluate for left atrial appendage thrombus, although cardiac computed tomography (CT) angiography using delayed acquisition imaging has been demonstrated to have excellent sensitivity and specificity as well.

CARDIOVERSION AND ANTICOAGULATION

The major source of thromboembolism and stroke in nonvalvular AF is formation of thrombus in the left atrial appendage where flow is relatively stagnant, although thrombus occasionally forms in other locations as well, particularly in patients with mitral valvular disease and severely dilated left atrium. Following conversion from prolonged AF to sinus rhythm, atrial mechanical function can be delayed for weeks (i.e., atrial stunning), such that thrombi can form even during sinus rhythm. When AF has been present for >48 h and in patients at high risk for thromboembolism, such as those with mitral stenosis or hypertrophic cardiomyopathy, conversion to sinus rhythm is associated with an increased risk of thromboembolism. Thromboembolism can occur soon or several days after restoration of sinus rhythm if appropriate anticoagulation measures are not taken. In patients with AF and left atrial appendage closure devices (e.g., Watchman device), electrical cardioversion is feasible without the need for oral anticoagulation if preprocedural transesophageal echocardiography shows good device position, absence of device-related thrombus, and peri-device leak of ≤5 mm.

Cardioversion *within 48 h of the onset of AF* without TEE or cardiac CT is common practice in patients who have not been anticoagulated, provided that they are not at high risk for stroke due to a prior history of embolic events, rheumatic mitral stenosis, or hypertrophic cardiomyopathy with marked left atrial enlargement. These low-risk patients with occasional episodes of AF can be instructed to notify their physician when AF occurs to arrange for cardioversion to be done within 48 h.

If the duration of AF exceeds 48 h or is unknown, there is greater concern for thromboembolism after cardioversion, even in patients considered low risk (CHA₂DS₂-VASc of 0 or 1 [see below]) for stroke. There are two approaches to mitigate the risk related to cardioversion. One option is to anticoagulate continuously for 3 weeks before and a minimum of 4 weeks after cardioversion. A second more frequently used approach is to start anticoagulation and perform a TEE or high-resolution cardiac CT scan to detect the presence of thrombus in the left atrial appendage. If thrombus is absent, electrical or pharmacologic cardioversion can be performed and anticoagulation continued for a minimum of 4 weeks to allow time for recovery of atrial mechanical function. In either case, cardioversion of AF is associated with a substantial risk of recurrence, which may not be symptomatic. It should be noted that these recommendations for short-term anticoagulation and thrombus exclusion at the time of cardioversion lack contemporary robust data to support these strategies. Longer-term maintenance of anticoagulation is considered based on the patient's individual risk for stroke, commonly assessed using the CHA₂DS₂-VASc score.

ACUTE RATE CONTROL

The goal of rate control in AF is to allow more diastolic filling time, improving cardiac output and reducing patient symptoms. In the longer term, adequate rate control will minimize the risk of congestive heart failure and tachycardia-induced cardiomyopathy. Acute rate control can be achieved with beta blockers and/or the calcium channel blockers verapamil and diltiazem administered either intravenously or orally, as warranted by the urgency of the clinical situation. Digoxin has been used for several years for rate control, particularly in patients with labile blood pressure and in patients with cardiomyopathy susceptible to congestive heart failure, because it lacks the negative inotropic effect seen in calcium channel blockers and beta blockers. It acts synergistically with beta blockers and calcium channel blockers and, therefore, may be useful as an added agent when rate control is inadequate. However, recent evidence suggests increased mortality with its chronic use, and so its utilization has declined.

CHRONIC RATE CONTROL

For patients who remain in AF chronically, the goal of rate control is to both alleviate symptoms and prevent deterioration of ventricular function from excessive rates. β -Adrenergic blockers and calcium channel blockers are often used either alone or in combination. Exertion-related symptoms are often an indication of inadequate rate control. Rate should be assessed with exertion and medications adjusted accordingly. Adequate rate control is defined as a resting heart rate of <80 beats/min that increases to <100 beats/min with light exertion, such as walking. If it is difficult to slow the ventricular rate to that degree, allowing a resting rate of up to 110 beats/min is acceptable provided it does not cause symptoms and ventricular function is normal; however, periodic assessment of ventricular function is warranted because some patients develop tachycardia-induced cardiomyopathy. In patients with permanent atrial fibrillation, a lenient rate-control strategy (resting heart rate <110 beats/min) is as effective as strict rate-control strategy (resting heart rate <80 beats/min and heart rate during moderate exercise <110 beats/min) in terms of death from cardiovascular causes, hospitalization for heart failure and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events, and this strategy is easier to achieve.

If adequate rate control in AF is difficult to achieve, further consideration should be given to restoring sinus rhythm (see below). Catheter ablation of the AV junction to create permanent AV block and implantation of a permanent pacemaker reliably achieve rate control without the need for AV nodal-blocking agents, a so-called “ablate and pace” strategy. These patients not only remain in AF but also become dependent on the pacemaker to support ventricular rate. The typical pacing configuration with placement of a ventricular lead in the right ventricular apex may induce dyssynchronous ventricular activation that can depress ventricular function in some patients. Biventricular pacing or direct pacing of the left bundle branch area may be used to minimize the degree of ventricular dyssynchrony. AV nodal ablation and cardiac resynchronization therapy have been demonstrated to be superior to pharmacologic therapy in improving quality of life and in reducing the development of heart failure, heart failure hospitalizations, and all-cause mortality in patients with permanent AF and a narrow QRS, irrespective of their baseline left ventricular ejection fraction.

STROKE PREVENTION IN ATRIAL FIBRILLATION

Thromboembolic complications, in particular, stroke, are the most significant and potentially life-threatening sequelae of AF. Therefore, appropriate stroke prevention strategies are a key aspect of AF management. The mainstay of stroke prevention is continuous anticoagulation therapy, most commonly using an oral medication. Specific patient populations have a high risk of stroke, including patients with hypertrophic cardiomyopathy, mitral stenosis, and prior stroke history, and therefore, anticoagulation is recommended, barring contraindications. AF in patients without mitral stenosis is commonly referred to as nonvalvular AF. In most patients with AF, the decision about whether a stroke prevention regimen is indicated is largely based on an assessment of stroke risk, balanced by the risk of the preventative therapy. The risk of stroke appears to be most accurately predicted by the presence of underlying risk factors known to increase stroke risk. The CHA₂DS₂-VASc scoring system (Fig. 258-3) is a widely used tool to estimate stroke risk. Anticoagulation is currently recommended in the United States and Europe for patients with a score of ≥ 1 unless the lone risk factor is female gender. Stroke risk increases with increasing CHA₂DS₂-VASc score, such that annual stroke risk may be as high as nearly 20% without anticoagulation. On the other hand, anticoagulation carries a risk of serious and potentially life-threatening bleeding complications, in particular, intracranial hemorrhage and gastrointestinal bleed. Bleeding risk is often assessed using the HAS-BLED scoring system (Fig. 258-3). If bleeding risk is deemed to be outweighed by stroke risk, anticoagulation is recommended. It is important to note the conventional wisdom that the *perceived* burden of AF has not been shown to predict stroke risk. The

CHA ₂ DS ₂ -VASc		HAS-BLED	
Risk Criteria			
Congestive heart failure	1	Hypertension	1
Age >75	2	Abnormal renal or liver function	1 each
Hypertension	1	Stroke history	1
Diabetes mellitus	1	Bleeding diathesis	1
Prior stroke or TIA	2	Labile INR (on warfarin)	1
Vascular disease	1	Elderly (Age >65)	1
Age >65	1	Drugs that predispose to bleeding or alcohol	1 each
Sex category (F)	1		

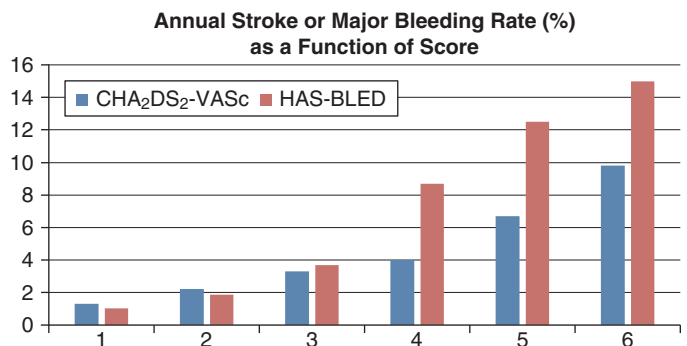


FIGURE 258-3 CHA₂DS₂-VASc and HAS-BLED systems. The CHA₂DS₂-VASc scoring system gives a point for each outlined stroke risk factor, whereas the HAS-BLED scoring system gives a point for each bleeding risk factor, as outlined in the table. In the chart below the table, the corresponding risk of stroke (CHA₂DS₂-VASc) or major bleed event (HAS-BLED) is plotted as a percent risk per annum as a function of score. F, female; INR, international normalized ratio; TIA, transient ischemic attack.

approach to patients with paroxysmal AF is therefore the same as for persistent AF. It is recognized that many patients who appear to have infrequent AF episodes based on office visits often have asymptomatic episodes that put them at risk. Absence of AF during periodic monitoring is not sufficient to indicate low risk. The role of continuous monitoring with implanted recorders or pacemakers as a guide for anticoagulation in patients with a borderline risk profile is not clear. Subclinical AF is short-lasting and asymptomatic and can usually be detected only by long-term continuous monitoring with implantable loop recorders, pacemakers, or defibrillators. Subclinical AF is associated with an increased risk of stroke by a factor of 2.5. In patients with subclinical AF lasting 6 min to 24 h, apixaban has been shown to decrease the risk of stroke or systemic embolism but increases the risk of major bleeding. Therefore, a more accurate accounting for the impact of AF burden on stroke risk remains to be clarified.

Antiplatelet agents alone are generally not sufficient. In nonvalvular AF, warfarin reduces the annual risk of stroke by 64% compared to placebo and by 37% compared to antiplatelet therapy. Patients with AF with an increased risk of stroke also have an increased risk of venous thromboembolism, which appears to be lower with oral anticoagulation. The direct-acting anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban were noninferior to warfarin in individual trials of nonvalvular AF patients, and intent-to-treat analysis of pooled data suggests superiority to warfarin by small absolute margins of 0.4–0.7% in reduction of mortality, stroke, major bleeding, and intracranial hemorrhage. Warfarin is required for patients with rheumatic mitral stenosis or mechanical heart valves. Among patients with rheumatic heart disease-associated AF, warfarin therapy has led to a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without

a higher rate of bleeding. Similarly, apixaban and dabigatran have failed to demonstrate noninferiority to warfarin and are less effective than warfarin for the prevention of valve thrombosis or thromboembolism in patients with mechanical heart valves.

Warfarin can be an inconvenient agent that requires several days to achieve a therapeutic effect (prothrombin time [PT]/international normalized ratio [INR] >2), requires monitoring of PT/INR to adjust dose, and has many drug and food interactions that can hinder patient compliance and render maintaining a therapeutic effect challenging. The direct-acting agents are easier to use and achieve reliable anticoagulation promptly without requiring dosage adjustment based on blood tests. Dabigatran, rivaroxaban, and apixaban have renal excretion and require dose adjustment for modest renal impairment, which is of particular concern in the elderly, who are at increased bleeding risk. Limited experience with apixaban and rivaroxaban demonstrates safety and efficacy in patients undergoing chronic hemodialysis for end-stage kidney disease. Excretion can also be influenced by P-glycoprotein inducers and inhibitors. Warfarin anticoagulation can be reversed by administration of fresh frozen plasma, prothrombin complex concentrate, and vitamin K. Reversal agents are available for dabigatran (idarucizumab), and Xa inhibitors are available (andexanet alfa), and both are administered intravenously. These agents may be prothrombotic, and administration must be judicious. The antiplatelet agents aspirin and clopidogrel are inferior to warfarin for stroke prevention in AF and do not have less risk of bleeding. Clopidogrel combined with aspirin is better than aspirin alone for stroke prevention, but this combination is inferior to warfarin and has a greater bleeding risk than aspirin alone.

Bleeding is the major risk of anticoagulation. Major bleeding requiring transfusion and intracranial bleeding occur in ~1% of patients per year with warfarin. Direct-acting anticoagulants appear to have a lower risk of intracranial bleeding compared with warfarin without sacrificing protective effects against thromboembolism. Risk factors for bleeding include age >65–75 years, heart failure, renal insufficiency, prior bleeding, and excessive alcohol or non-steroidal anti-inflammatory drug use. In patients who require dual antiplatelet therapy (e.g., aspirin and clopidogrel) after coronary or peripheral arterial stenting, there is a substantially increased bleeding risk when standard oral anticoagulation with warfarin or a direct-acting anticoagulant is added. In AF patients undergoing percutaneous coronary intervention, the combination of oral platelet inhibition with a P2Y₁₂ inhibitor (preferably clopidogrel) is recommended. Triple antithrombotic therapy, preferably including a direct-acting anticoagulant, should be considered in patients with high ischemic risk (e.g., acute coronary syndrome) and for up to 30 days.

Chronic anticoagulation is contraindicated in some patients due to bleeding risks. Because most atrial thrombi likely originate in the left atrial appendage, surgical removal of the appendage, combined with atrial maze surgery, may be considered for patients undergoing surgery, although removal of the appendage has not been unequivocally shown to reduce the risk of thromboembolism. Percutaneously deployed devices that occlude or ligate the left atrial appendage are also available, appear to be noninferior to warfarin in reducing stroke risk, and are considered in patients who have a high risk of thromboembolism but serious bleeding risk from

chronic oral anticoagulation (Table 258-2). Importantly, left atrial appendage closure devices (i.e., Watchman) provide stroke prevention comparable to warfarin, with additional significant reductions in major bleeding, particularly hemorrhagic stroke, and all-cause mortality. Furthermore, left atrial appendage closure devices appear to be noninferior to direct-acting anticoagulants in preventing major AF-related cardiovascular, neurologic, and bleeding events.

RHYTHM CONTROL

The decision to administer antiarrhythmic drugs or perform catheter ablation to attempt maintenance of sinus rhythm (commonly referred to as the *rhythm control strategy*) is mainly guided by patient symptoms and preferences regarding the benefits and risks of therapies. In general, patients who maintain sinus rhythm have better survival than those who continue to have AF. This may be because continued AF is a marker of disease severity or that AF promotes deterioration in cardiac function. In older randomized trials, administration of antiarrhythmic medications to maintain sinus rhythm did not improve survival or symptoms compared to a rate control strategy, and the drug therapy group had more hospitalizations. Disappointing efficacy and toxicities of available antiarrhythmic drugs, in retrospect inappropriate discontinuation of anticoagulation in the rhythm control arms, and patient selection bias may be factors that influenced the results of these trials. Recently, a randomized trial evaluating an early rhythm control strategy (within 1 year of initial presentation) compared to standard rate control demonstrated a reduction in cardiovascular events, including death from cardiovascular causes and stroke. Differences between this study and earlier randomized trials that failed to show a significant difference in outcomes in rate versus rhythm control included the use of catheter ablation and a high adherence rate to anticoagulation despite apparent rhythm control. In patients with heart failure due to depressed left ventricular function, a catheter ablation-based strategy to maintain sinus rhythm appears to provide all-cause mortality benefit compared with a medical rhythm control strategy. Furthermore, the combination of catheter ablation and guideline-directed medical therapy in patients with symptomatic AF and end-stage heart failure who are referred for heart transplantation evaluation is associated with a lower likelihood of a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation than medical therapy alone.

A rhythm control strategy is usually selected for patients with symptomatic paroxysmal AF, recurrent episodes of symptomatic persistent AF, AF with difficult rate control, and AF that has resulted in depressed ventricular function or that aggravates heart failure. A rhythm control strategy is more likely to be favored in younger patients than in sedentary or elderly patients in whom rate control is more easily achieved. Even if sinus rhythm is apparently maintained, anticoagulation is recommended according to the CHA₂DS₂-VASC stroke risk profile because asymptomatic episodes of AF are common. Following a first episode of persistent AF, a strategy using AV nodal-blocking agents, cardioversion, and anticoagulation is reasonable, in addition to addressing possible aggravating factors. If recurrences are infrequent, periodic cardioversion is reasonable. However, if a patient has frequent symptomatic AF despite rate control, then a rhythm control strategy incorporating

TABLE 258-2 Novel Oral Anticoagulant Dosing

	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Standard dose	150 mg bid	20 mg qd	5 mg bid	60 mg qd
Reduced dose	110 mg bid	15 mg qd	2.5 mg bid	30 mg qd
Dose reduction criteria	Dabigatran 110 mg bid in patients with: age ≥80 years, concomitant use of verapamil, or increased bleeding risk	Creatine clearance 15–49 mL/min	At least 2 of 3 criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 μmol/L)	If any of the following: creatinine clearance 30–50 mL/min, body weight ≤60 kg, or concomitant use of dronedarone, cyclosporine, erythromycin, or ketoconazole

Note: As of publication, four novel or direct oral anticoagulants are available and indicated for stroke prevention for atrial fibrillation. The standard dosing, reduced dosing, and criteria for reduced dosing are shown for each agent.

catheter ablation and/or antiarrhythmic medications is indicated. Based on recent randomized trial data demonstrating superiority of ablation over medications for maintenance of sinus rhythm and benefits of an early rhythm control strategy, catheter ablation is considered first-line therapy, especially for individuals with paroxysmal AF.

Pharmacologic Therapy for Maintaining Sinus Rhythm The goal of pharmacologic therapy is to maintain sinus rhythm or reduce episodes of AF. Risks and side effects of antiarrhythmic drugs are a major consideration in selecting therapy. Drug therapy can be instituted once sinus rhythm has been established or in anticipation of cardioversion. However, antiarrhythmic medications may in some instances pharmacologically cardiovert the patient into sinus rhythm. Therefore, an appropriate anticoagulation strategy approach similar to electrical cardioversion is recommended, particularly at the time of initiation of therapy. β -Adrenergic blockers and calcium channel blockers help control ventricular rate, improve symptoms, and possess a low-risk profile, but have low efficacy for preventing or terminating AF episodes. Class I sodium channel-blocking agents (e.g., flecainide, propafenone, disopyramide) are options for patients without significant structural heart disease, but negative inotropic and proarrhythmic effects warrant avoidance in patients with coronary artery disease or heart failure. The class III agents sotalol and dofetilide can be administered to patients with coronary artery disease or structural heart disease but have ~3% risk of inducing excessive QT prolongation and torsades des pointes. Dofetilide should be initiated only in a hospital with ECG monitoring, and many physicians take this approach with sotalol as well. Dronedaron increases mortality in patients with heart failure or long-standing persistent AF. All these agents have modest efficacy in patients with paroxysmal AF, of whom ~30–50% will benefit. Amiodarone is more effective, maintaining sinus rhythm in approximately two-thirds of patients. It can be administered to patients with heart failure and coronary artery disease. However, >40% of patients experience amiodarone-related toxicities during long-term therapy, and thus, careful monitoring of potential toxicities, including skin, liver, lung, and thyroid abnormalities, must be accompanied with this therapy.

Catheter and Surgical Ablation for Maintaining Sinus Rhythm Successful catheter ablation avoids antiarrhythmic drug toxicities, but procedural risks and efficacy depend on operator experience. For patients with previously untreated but recurrent paroxysmal AF, catheter ablation has superior efficacy compared to antiarrhythmic drug therapy, and ablation is even more clearly superior to antiarrhythmic drugs for patients who have recurrent AF despite drug treatment. Long-term control of AF is more difficult to achieve in patients with persistent and long-standing persistent AF, likely because of more extensive atrial abnormalities and associated greater comorbidities in these patients that may promote ongoing progression of atrial abnormalities that in turn promote AF recurrence.

Catheter ablation involves percutaneous venous access (typically via the femoral veins), trans (atrial) septal puncture, and radiofrequency ablation or cryoablation to electrically isolate the left atrial regions around the pulmonary vein antra, abolishing the ability of triggering foci in these regions to initiate AF and also likely impacting the substrate for reentry in the left atrium (Fig. 258-4). Gaps in healed ablation areas or emergence of new trigger sites outside the pulmonary veins necessitate a repeat procedure in 10–30% of patients. Several alternative energy sources to create ablative lesions are being evaluated for ablation of AF and other arrhythmias, including laser, external beam radiation, and pulsed field electroporation.

Pulsed-field ablation uses electric fields generated by short pulses of high energy and has shown promise by specifically targeting myocardium without generating heat or damaging adjacent tissue (Fig. 258-5). Myocardial cells are uniquely sensitive to high-voltage, short-duration electric fields with electroporation thresholds of 268–375 V/cm compared to other tissue types including nerves, endothelium, vascular smooth muscle, and blood cells, all of which have electroporation thresholds >1600 V/cm. The pulse waveforms used to generate an electric field can have many different characteristics including voltage amplitude, pulse width, cycle period, voltage polarity (monophasic vs. biphasic), electrode polarity (unipolar vs. bipolar), and the number of pulses delivered in a train. There are limited data evaluating the impact of how each of these variables affect lesion safety and efficacy (Fig. 258-5). Therefore, unlike radiofrequency ablation, pulsed-field ablation in its current clinical iteration lacks the ability to titrate and tailor energy delivery during ablation.

In patients with paroxysmal AF, sinus rhythm is maintained for >1 year after a single ablation procedure in ~80% of patients and is achieved in >90% of patients after multiple procedures in some studies. Among patients with paroxysmal AF receiving a catheter-based therapy, pulsed-field ablation has demonstrated to be noninferior to conventional thermal ablation (i.e., radiofrequency ablation and cryoablation) with respect to freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation and with respect to device- and procedure-related serious adverse events at 1 year.

Many patients become more responsive to antiarrhythmic drugs or become less symptomatic with a reduced AF burden after a pulmonary vein isolation procedure, and thus, repeat ablation may not be required for symptom control in some. Ablation is less effective in patients with persistent AF, particularly long-standing persistent AF, especially when associated with more extensive cardiac disease, comorbidities, and evidence of moderate and severe left atrial enlargement. More extensive ablation is often required, targeting areas that likely support reentry and/or AF maintenance and regions outside but adjacent to the pulmonary venous antra.

Most ablation targets and strategies beyond pulmonary vein isolation have failed to show systematic outcome improvement in randomized controlled clinical trials. However, individualized

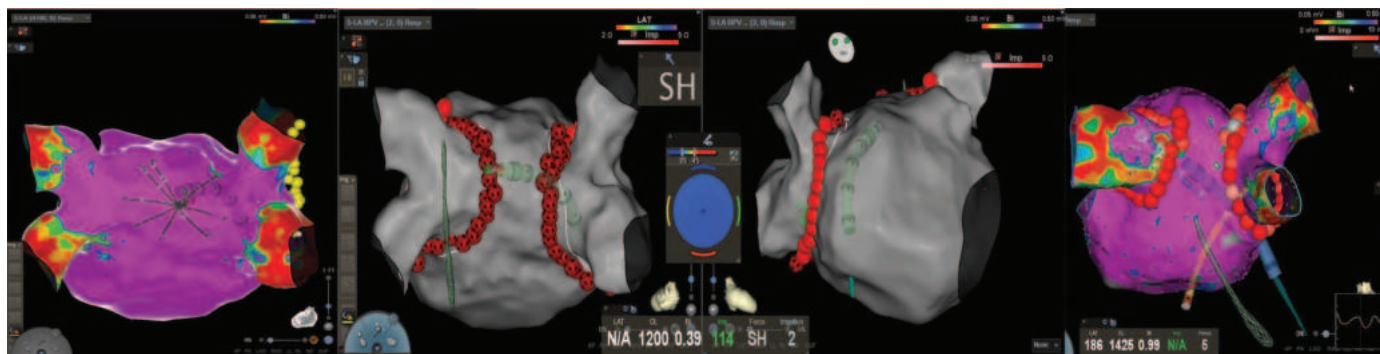


FIGURE 258-4 **A.** (Left) Electroanatomic map superimposed on a cardiac computed tomography reconstruction of a left atrium with mapping catheter in the posterior wall of this chamber. (Middle) Final radiofrequency lesion set around the pulmonary veins. (Right) Multipolar catheter in the right inferior pulmonary vein **B.** Spontaneous pulmonary vein (PV) ectopy initiating fibrillatory conduction contained within the isolated vein while 12-lead electrocardiogram shows normal sinus rhythm.

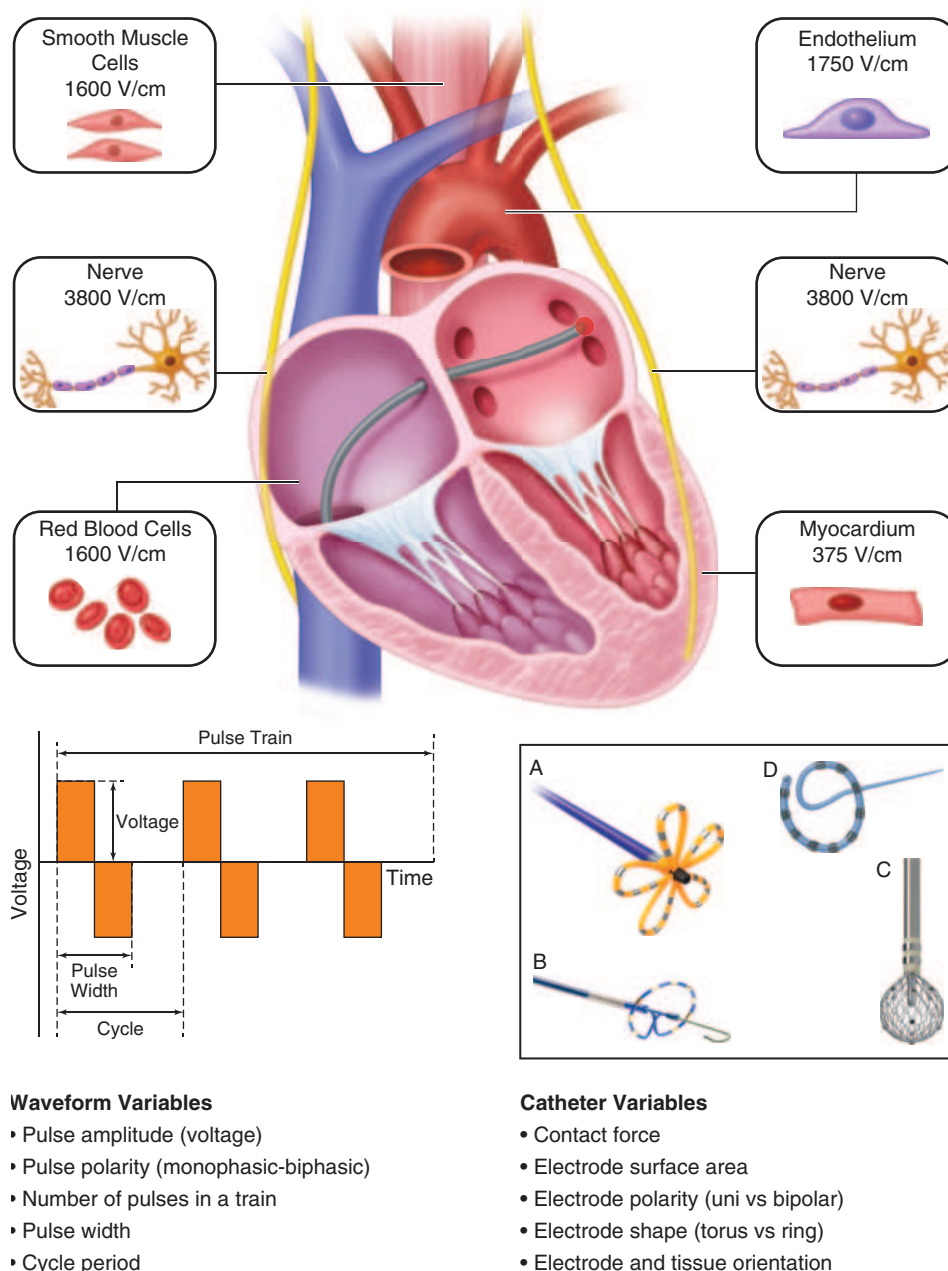


FIGURE 258-5 Pulsed-field electroporation. (Top) Pulsed-field ablation has the potential to target specifically myocardial tissue without negatively affecting adjacent structures or cells such as red blood cells, nerves, the esophagus, or arteries. (Bottom) Numerous factors are involved in creating long-lasting transmural lesions with pulse-field ablation; a combination of most of these parameters will eventually help in delivering electroporation effectively and safely into the myocardial tissue. Catheters currently undergoing clinical evaluation for pulsed-field ablation (PFA). (Reproduced from CD Matos et al: Pulsed Field Ablation of Atrial Fibrillation: A Comprehensive Review. *Rev Cardiovasc Med* 24:337, 2023 and Reproduced with permission from NA Steiger, JE Romero. Pulsed-field ablation: What are the unknowns and when will they cease to concern us. *J Cardiovasc Electrophysiol* 33:1489, 2022.) (A) Farawave, reproduced with permission from Boston Scientific; (B) PVAC, reproduced with permission from Medtronic; (C) Sphere-9, reproduced with permission from Medtronic; (D) Varipulse.

ablation of atrial low-voltage myocardium in addition to pulmonary vein isolation significantly improved outcomes in patients with persistent AF in one study. Similarly, in patients with persistent AF, treatment with combined catheter ablation and vein of Marshall ethanol infusion had better outcomes compared with catheter ablation alone. Ablation of areas of rapid activity during AF and creation of empiric ablation lines to block conduction across regions of the atria have not been proven to improve outcomes in unselected patients. Other ablation targets include non-pulmonary vein foci that fire in response to high-dose isoproterenol and regions with repetitive rotational or focal activation during AF. More than one ablation procedure is often required to maintain sinus rhythm in patients with persistent and long-standing persistent AF because of lack of lesion durability and complex atrial substrate with non-pulmonary vein sources that may be incompletely treated at the initial ablation session (Table 258-3).

Catheter ablation has a 2–7% risk of major procedure-related complications, with the long-term trend suggesting steady improvement in complication rates. Complication rates are clearly lowest with high-volume operators and centers. Complications include stroke (0.5–1%), cardiac tamponade (1%), phrenic nerve paralysis, bleeding from femoral access sites, and fluid overload with heart failure, which can emerge 1–3 days after the procedure. It is important to recognize the potential for delayed presentation of some complications. Ablation within the pulmonary vein can lead to pulmonary vein stenosis, presenting weeks to months after the procedure with dyspnea or hemoptysis. The esophagus abuts the posterior wall of the left atrium where it is subject to injury, and esophageal ulcers can form immediately after the procedure and may rarely lead to a fistula between the left atrium and esophagus (estimated incidence of <0.1%) that presents as endocarditis and stroke 10 days to 3 weeks after the procedure. Early diagnosis

TABLE 258-3 Recommendations for Catheter Ablation in Patients with Atrial Fibrillation (AF)

CLASS	LEVEL OF EVIDENCE	RECOMMENDATIONS
1	A	In patients with symptomatic AF in whom antiarrhythmic drugs have been ineffective, contraindicated, not tolerated or not preferred, and continued rhythm control is desired, catheter ablation is useful to improve symptoms.
1	A	In selected patients (generally younger with few comorbidities) with symptomatic paroxysmal AF in whom rhythm control is desired, catheter ablation is useful as first-line therapy to improve symptoms and reduce progression to persistent AF.
1	A	In patients with symptomatic or clinically significant atrial flutter, catheter ablation is useful for improving symptoms.
2a	B	In patients who are undergoing ablation for AF, ablation of additional clinically significant supraventricular arrhythmias can be useful to reduce the likelihood of future arrhythmia.
2a	B	In patients (other than younger with few comorbidities) with symptomatic paroxysmal or persistent AF who are being managed with a rhythm-control strategy, catheter ablation as first-line therapy can be useful to improve symptoms.

Source: Reproduced with permission from JA Joglar et al: 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 83:109, 2024.

of atrioesophageal fistula is important because delayed diagnosis leads to likely death. Diagnosis is made by chest CT scan with water-soluble oral and IV contrast. Endoscopy should be avoided in patients with a suspected fistula because of the risk of air/esophageal fluid embolus. Definitive repair of the atrioesophageal fistula with emergent surgery is required. Pulsed-field ablation is associated with a significantly reduced risk of pulmonary vein stenosis, phrenic nerve injury, and left atrial esophageal fistula.

Surgical ablation of AF is most frequently performed concomitant with cardiac valve or coronary artery surgery and less commonly as a stand-alone procedure. There is no significant difference in the rate of freedom from AF between patients who undergo pulmonary vein isolation and those who undergo the biatrial maze procedure.

However, for patients with persistent AF, surgical or hybrid procedures (a combination of a surgical and catheter-based approach, most often in separate procedures) appear to have comparable efficacy to catheter ablation. Risks include sinus node injury requiring pacemaker implantation and higher morbidity with surgical ablation. Surgical removal of the left atrial appendage may reduce stroke risk, although thrombus can form in the remnant of the appendage or if the appendage is not completely ligated.

RISK FACTORS FOR AND LIFESTYLE IMPACT ON ATRIAL FIBRILLATION

There is strong evidence that AF is associated with a sedentary lifestyle, obesity, hypertension, smoking, alcohol use, and sleep apnea. Aggressive treatment of these risk factors can substantially reduce AF episodes in some patients and is warranted in all patients, as additional benefits to the patient are likely beyond AF improvement. The amount of exercise appears to have a complex relationship with the risk of AF development. In males, a U-shaped curve exists, where AF risk is high among those with sedentary lifestyles and those who participate extensively in endurance athletics such as long-distance running or cycling. Moderate exercise appears to confer a lower risk of AF. On the other hand, in females, a linear relationship exists between exercise and AF risk, with risk of AF decreasing continuously with increasing exercise activity. Although caffeine intake is often invoked as a risk for AF development or as a trigger for AF episodes in patients with a known AF diagnosis, large cohort studies have demonstrated, in contrast, a modest decrease in AF risk with modest caffeine intake. Other proposed risk factors are

being evaluated, including psychological stress. Genetic predisposition to AF is seen in those with first-degree relatives with AF, and a small subset of AF patients can be determined have a familial form of AF.

There is emerging emphasis on an integrated approach to management of AF patients, with coordinated management of risk factor modification, stroke prevention, rate control, rhythm control, and management of associated comorbidities of critical importance. The previous classification of AF, which was based only on arrhythmia duration (i.e., paroxysmal, persistent, and long-standing persistent), although useful, tended to emphasize therapeutic interventions. A more recent classification using four stages (i.e., at risk of AF, pre-AF, AF, and permanent AF) has been proposed and recognizes AF as a disease continuum that requires a variety of strategies at the different stages, including prevention, lifestyle and risk factor modification, screening, and therapy.

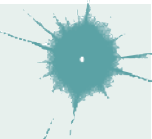
FURTHER READING

JOGLAR JA et al: 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 83:109, 2024.
PACKER DL et al: Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: The CABANA randomized clinical trial. JAMA 321:1261, 2019.

259

Approach to Ventricular Arrhythmias

William H. Sauer, Usha B. Tedrow



There are myriad types of ventricular arrhythmias (VAs), ranging from benign to life-threatening, occurring both in patients with normal hearts and in those with structural heart disease. An understanding of an approach to these arrhythmias is critical to being appropriately parsimonious with benign forms, while understanding timely workup and management of the malignant forms.

TYPES OF VAs

VAs can arise from focal sites of origin or from reentrant circuits. Focal VAs can originate from myocardial or specialized Purkinje cells capable of automaticity or triggered activity. Reentrant VAs often involve areas of scar such as old myocardial infarction or a cardiomyopathic process. Less commonly, diseased Purkinje conduction pathways can also result in reentrant circuits. VAs are characterized by their electrocardiographic appearance and duration. Conduction away from the ventricular focus or reentrant circuit exit, propagating through the ventricular myocardium, is slower than activation of the ventricles over the normal Purkinje system. For this reason, the QRS complex duration during VAs will be wide, typically >0.12 s, though there are unusual situations that can arise with narrow QRS duration as well.

Premature ventricular beats (also referred to as a premature ventricular contractions or premature ventricular complexes [PVCs]) are single ventricular beats that occur earlier than the next anticipated supraventricular beat (Fig. 259-1). PVCs that originate from the same focus will have the same QRS morphology and are referred to as unifocal (Fig. 259-1A). PVCs that originate from different ventricular sites have different QRS morphologies and are referred to as multifocal (Fig. 259-1B). Two consecutive ventricular beats are ventricular couplets.

Ventricular tachycardia (VT) is three or more consecutive beats at a rate faster than 100 beats/min. Three or more consecutive beats at

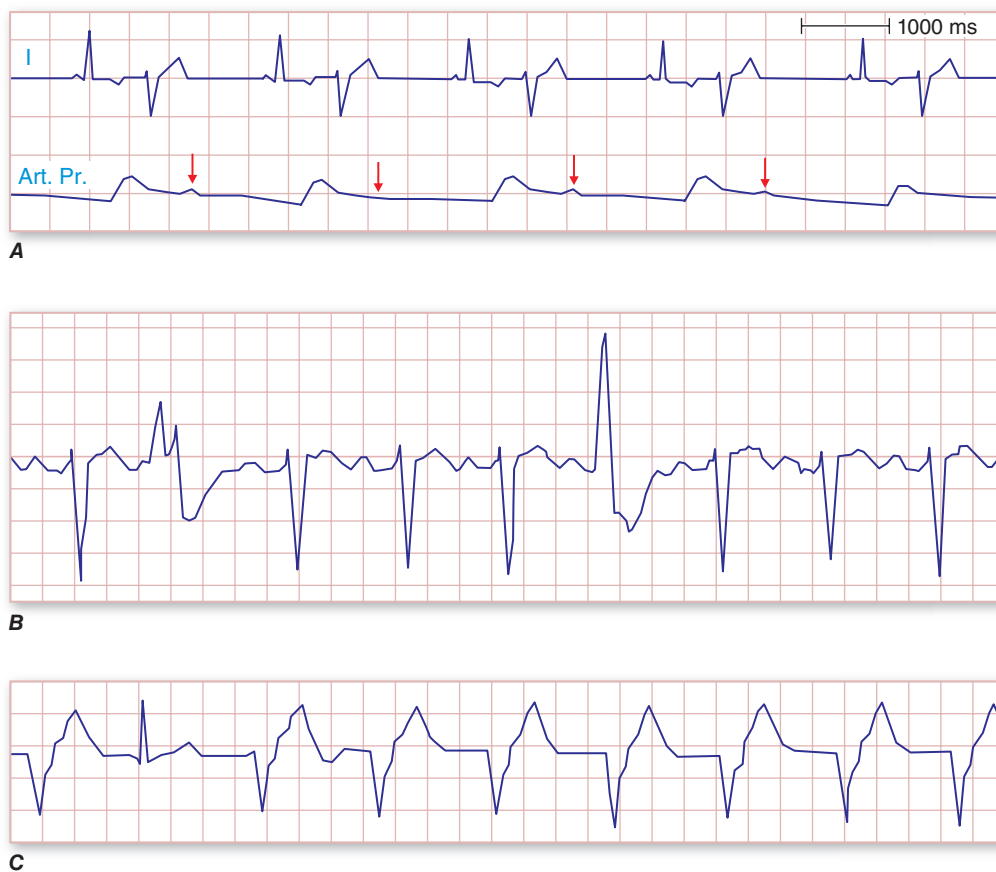


FIGURE 259-1 **A.** Unifocal premature ventricular contractions (PVCs) at bigeminal frequency. Trace shows electrocardiogram lead 1 and arterial pressure (Art. Pr.). Sinus rhythm beats are followed by normal arterial waveform. The arterial pressure following premature beats is attenuated (arrows) and imperceptible to palpation. The pulse in this patient is registered at half the heart rate. **B.** Multifocal PVCs. The two PVCs shown have different morphologies. **C.** Example of accelerated idioventricular rhythm. (See text for details.)

slower rates are designated an idioventricular rhythm. VT that terminates spontaneously within 30 s is designated *nonsustained*, whereas sustained VT persists for >30 s or is terminated by an active intervention, such as administration of an intravenous medication, external

cardioversion, antitachycardia pacing, or a shock from an implanted cardioverter-defibrillator (**Fig. 259-2**).

Monomorphic VT has the same QRS complex from beat to beat, indicating that the activation sequence is the same from beat to beat

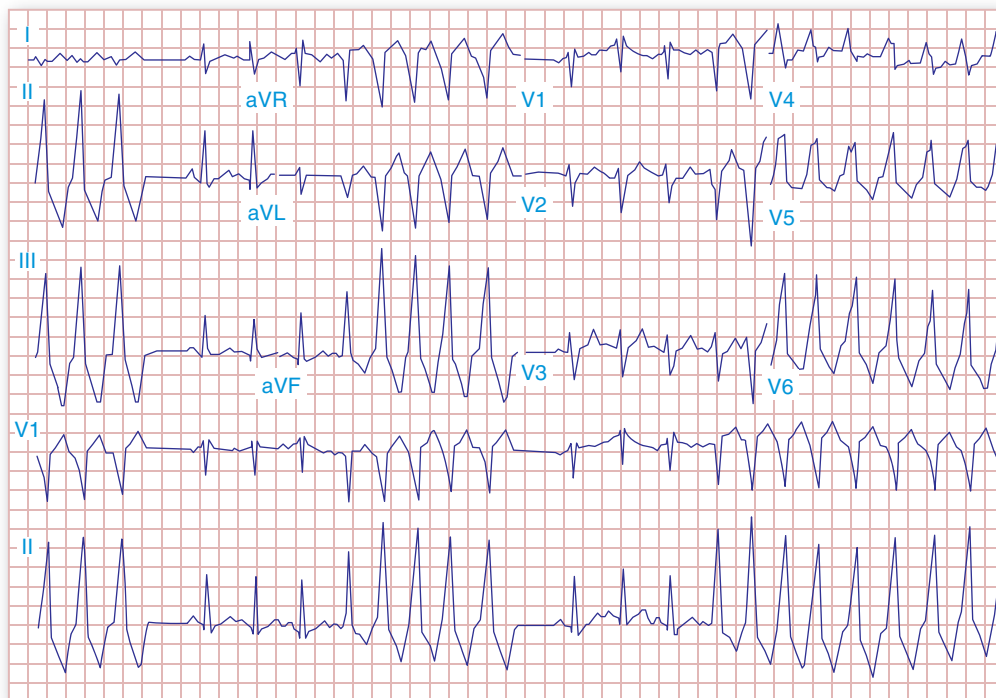


FIGURE 259-2 Repetitive monomorphic nonsustained ventricular tachycardia (VT) of right ventricular outflow tract origin. The VT has a left bundle branch block pattern with inferior axis with tall QRS complexes in the inferior leads.

and that each beat likely originates from the same source (Fig. 259-3A). The initial site of ventricular activation largely determines the sequence of ventricular activation. Therefore, the QRS morphology of PVCs and monomorphic VT provides an indication of the site of origin within the ventricles (Fig. 259-4). The likely origin often suggests whether an arrhythmia is idiopathic or associated with structural disease. Arrhythmias that originate from the right ventricle or septum result in late activation of much of the left ventricle, thereby producing a prominent S wave in V_1 referred to as a left bundle branch block–like configuration. Arrhythmias that originate from the free wall of the left ventricle have a prominent positive deflection in V_1 , thereby producing a right bundle branch block–like morphology in V_1 . The frontal plane axis of the QRS is also useful. An axis that is directed inferiorly, as indicated by dominant R waves in leads II, III, and AVF, suggests initial activation of the cranial portion of the ventricle, whereas a frontal plane axis that is directed superiorly (dominant S waves in II, III, and AVF) suggests initial activation at the inferior wall.

Very rapid monomorphic VT has a sinusoidal appearance, also called *ventricular flutter*, because it is not possible to distinguish the QRS complex from the T wave (Fig. 259-3B). Relatively slow *sinusoidal* VTs have a wide QRS indicative of slowed ventricular conduction (Fig. 259-3C). Hyperkalemia, toxicity from excessive effects of drugs that block sodium channels (e.g., flecainide, propafenone, or tricyclic antidepressants), and severe global myocardial ischemia are possible causes.

Polymorphic VT has a continually changing QRS morphology indicating a changing ventricular activation sequence. Polymorphic VT that occurs in the context of congenital or acquired prolongation of the QT interval often has a waxing and waning QRS amplitude, creating a characteristic shifting axis referred to as *torsades des pointes* after the classic ballet sequence (Fig. 259-3D).

Ventricular fibrillation (VF) has continuous irregular activation with no discrete QRS complexes. Monomorphic or polymorphic VT may transition to VF in susceptible patients. Cardiac ischemia is the most common cause of VF (Fig. 259-3E).

The term *idiopathic ventricular arrhythmia* generally refers to PVCs or VT that occurs in patients with a normal electrocardiogram (ECG), without structural heart disease, and not associated with an underlying genetic syndrome or risk of sudden death.

CLINICAL MANIFESTATIONS

Common symptoms of VAs include palpitations, dizziness, exercise intolerance, episodes of lightheadedness, syncope, or sudden cardiac arrest leading to sudden death if not resuscitated. VAs can also be asymptomatic and encountered unexpectedly as an irregular pulse or heart sounds on examination or may be seen on a routine ECG, exercise test, or cardiac ECG monitoring. Occasionally when every other beat is a PVC (*bigeminy*), pulse measurements for heart rate can be erroneously low (*pseudobradycardia*) because the PVCs may not generate a separate pulse wave.

Syncope is a concerning symptom, particularly when occurring without prodrome, during exercise, or in the setting of abnormal ECG or structural heart disease. Such episodes can be due to VT that produces severe hypotension, warranting concern for risk of cardiac arrest and sudden death with arrhythmia recurrence. Although benign processes such as reflex-mediated neurocardiogenic (vasovagal) episodes and orthostatic hypotension are the most common causes of syncope, it is important to consider the possibility of underlying heart disease or a genetic syndrome causing VT. When these are suspected, hospitalization for further evaluation and monitoring is often appropriate.

Sustained VT may present as a wide QRS complex tachycardia that must be distinguished from supraventricular tachycardia with aberrancy (Chap. 253). Symptoms can be minor but more commonly include hypotension with syncope and even imminent cardiac arrest, particularly in patients with structural heart disease. Sustained VT may degenerate to VF, most commonly if it is rapid and polymorphic. Many patients who are at risk for VT have known heart disease, and many have an implantable cardioverter-defibrillator (ICD). In patients with an ICD, VT episodes may cause transient lightheadedness, palpitations, or syncope followed by a shock from the ICD (see below).

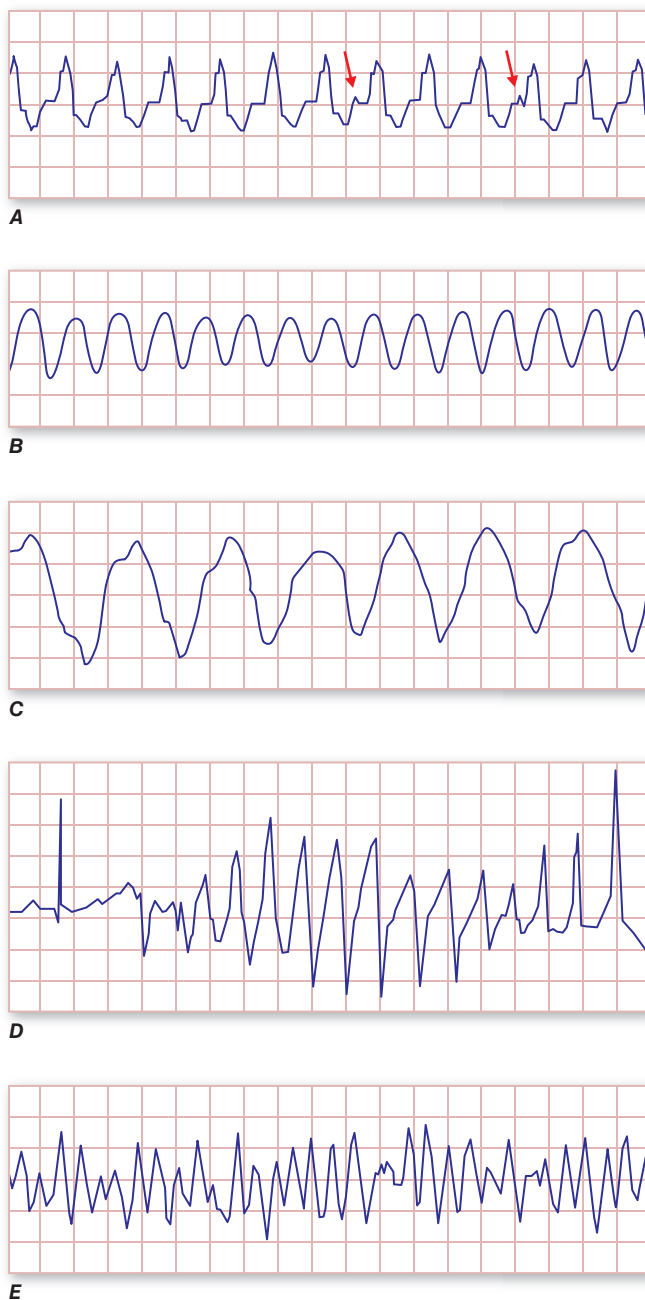


FIGURE 259-3 A. Monomorphic ventricular tachycardia (VT) with dissociated P waves (short arrows). B. Ventricular flutter. C. Sinusoidal VT due to electrolyte disturbance or drug effects. D. Polymorphic VT resulting from prolongation of QT interval (torsade de pointe VT). E. Ventricular fibrillation. (See text for details.)

EVALUATION OF PATIENTS WITH DOCUMENTED OR SUSPECTED VENTRICULAR ARRHYTHMIAS

There are several important considerations that guide evaluation of patients with documented or suspected cardiac arrhythmias. First, establish whether a VA is the cause of the symptoms or clinical presentation. Second, determine whether the arrhythmia is associated with a cardiac disease, and establish the prognostic significance of that disease and, in particular, whether it is associated with a risk of sudden cardiac death. Finally, define the likelihood of arrhythmia recurrence and the symptoms and risk imposed by the recurrence. The risks of cardiac arrest and sudden cardiac death are largely determined by the cause of the arrhythmia and the associated underlying heart disease.

The diagnosis of VAs can be established by recording the arrhythmia on an ECG, by an ambulatory or implanted cardiac monitor, by an implanted rhythm management device such as a pacemaker or ICD, or in some cases, initiation of the arrhythmia during an electrophysiologic

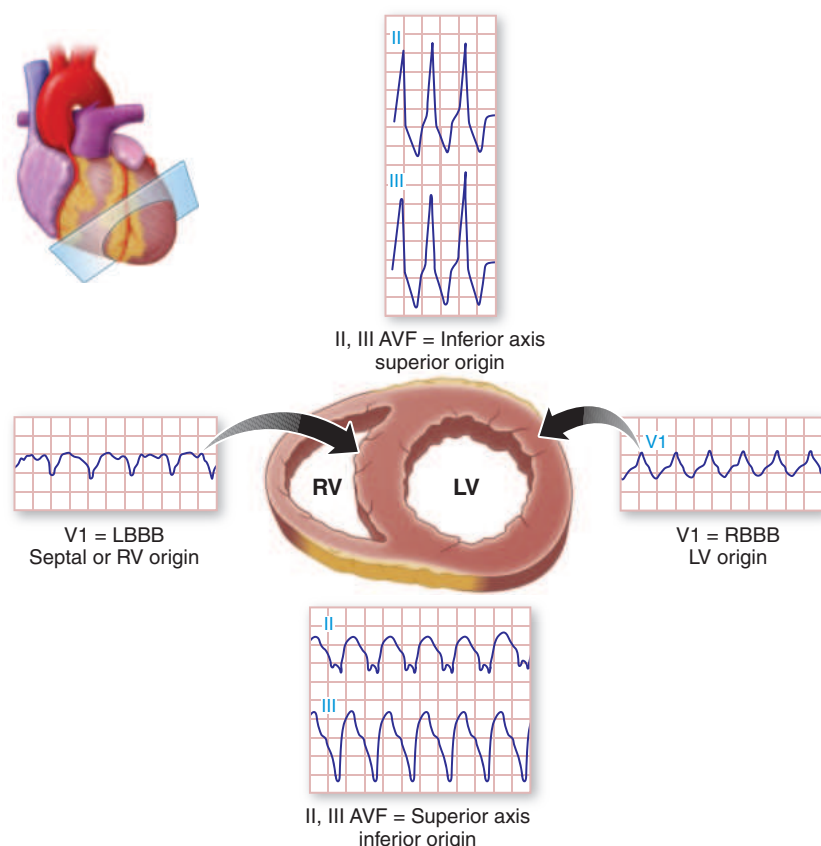


FIGURE 259-4 Site of ventricular tachycardia origin based on QRS morphology. (See text for details.) LBBB, left bundle branch block; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle.

study. A 12-lead ECG of the arrhythmia should be obtained when possible and often provides clues to the potential site of origin and possible presence of underlying heart disease (see above) (Fig. 259-4).

For patients with sustained wide-complex tachycardia, initial management is guided by the patient's hemodynamic stability. The approach to sustained wide-complex tachycardia is discussed in [Chap. 261](#). The management of VT that causes cardiac arrest is discussed in [Chap. 317](#). Once hemodynamic stability is restored, further management is guided by the possibility of a recurrence and the risk imposed by a recurrence.

■ EVALUATION OF THE PATIENT WITH ARRHYTHMIA SYMPTOMS

When symptoms are intermittent, initial evaluation aims to establish symptom severity, provocative factors, and presence of underlying heart disease. Syncope or near syncope raises concern that an arrhythmia is causing episodes of hypotension and that there may be a risk of cardiac arrest. Symptoms that occur with exertion suggest arrhythmias that are provoked by sympathetic stimulation but can also be related to exertional ischemia in patients with coronary artery disease, although nonarrhythmia causes must also be considered. A past history of any cardiac disease is important. A review of all medications is relevant. Medications that prolong the QT interval predispose to polymorphic VT ([Chap. 262](#)). Adrenergic stimulants can provoke PVCs.

Family history should determine the presence of premature coronary artery disease, cardiomyopathy, or cardiac arrhythmias, particularly a history of sudden death. Family history may also suggest that the possibility of a genetic cause of an arrhythmia warrants careful consideration. Details of premature deaths are relevant. Sudden death victims are often said to have died of a "massive heart attack" despite absence of definite confirmation of thrombotic myocardial infarction and when other causes such as arrhythmia may have been possible.

The physical examination focuses on evidence of structural heart disease with assessment of pulse, jugular venous pressure lung fields, and cardiac auscultation. Stigmata of neuromuscular disease or dysmorphic features may suggest a genetic arrhythmia syndrome.

A 12-lead ECG should be obtained even if the patient is not having symptoms at the time of evaluation. Occasionally, premature ventricular contractions will be detected. Patients with benign idiopathic arrhythmias usually have a completely normal ECG during sinus rhythm. Any ECG abnormality warrants further evaluation. Particularly relevant findings include Q waves that indicate prior myocardial infarction, which may have been silent, and ventricular hypertrophy, which may indicate hypertrophic cardiomyopathy or other ventricular disease. An ECG finding is the major diagnostic manifestation of several genetic arrhythmia syndromes in patients without structural heart disease, including the long QT syndrome, Brugada syndrome, and short QT syndrome.

If there is suspicion of structural heart disease, cardiac imaging is warranted to assess ventricular function and structure. Transthoracic echocardiography is most frequently employed for initial evaluation. Depressed ventricular function increases concern for a risk of sudden death and warrants further evaluation to establish the cause, which may be cardiomyopathy, coronary artery disease, or valvular heart disease. Ventricular thickening may indicate hypertrophic cardiomyopathy or infiltrative diseases such as amyloidosis. Cardiac magnetic resonance imaging with gadolinium contrast imaging provides similar assessment but also can detect areas of ventricular scar, evident as regions of delayed hyperenhancement, which are usually present in patients who have sustained monomorphic VT ([Fig. 259-5](#)). The nature and location of abnormalities are helpful in assessing the type of heart disease. Evaluation to

exclude atherosclerotic coronary artery disease should be performed in patients at risk, guided by age and other risk factors.

■ TREATMENT OPTIONS FOR VENTRICULAR ARRHYTHMIAS

Treatment of VAs is guided by the severity and frequency of symptoms. For those with structurally normal hearts and normal ECGs, reassurance and removal of aggravating factors (e.g., caffeine or alcohol) may be all that is needed. For arrhythmias associated with a sudden death risk, ICD implantation is usually indicated and will provide a "safety net" to terminate life-threatening VT or VF, preventing sudden death but without preventing the arrhythmia. When suppression of the arrhythmia is required, antiarrhythmic drug therapy or catheter ablation is a major consideration.

■ ANTIARRHYTHMIC DRUGS

Use of antiarrhythmic drugs is based on consideration of the risks and potential benefit for the individual patient. Efficacy and side effects for the individual patient are not always predictable and are assessed by individual therapeutic trial. Causes of drug intolerance are mostly non-cardiac and minor but can sometimes be severe enough to limit their use. Cardiac adverse events, however, include the potential for "proarrhythmia," whereby a drug can increase the frequency of arrhythmia or cause a new arrhythmia. Aggravation of bradyarrhythmias is also a common concern. Although antiarrhythmic drugs are classified based on their actions on receptors or ion channels, most have multiple effects, affecting more than one channel.

■ β -ADRENERGIC BLOCKERS

Many VAs are sensitive to sympathetic stimulation, and β -adrenergic stimulation may also interact with the electrophysiologic effects of many membrane-active antiarrhythmic drugs. The safety of β -blocking agents makes them the first choice of therapy for most VAs. β -Blockers are particularly useful for exercise-induced arrhythmias and idiopathic arrhythmias but have limited efficacy for most arrhythmias associated

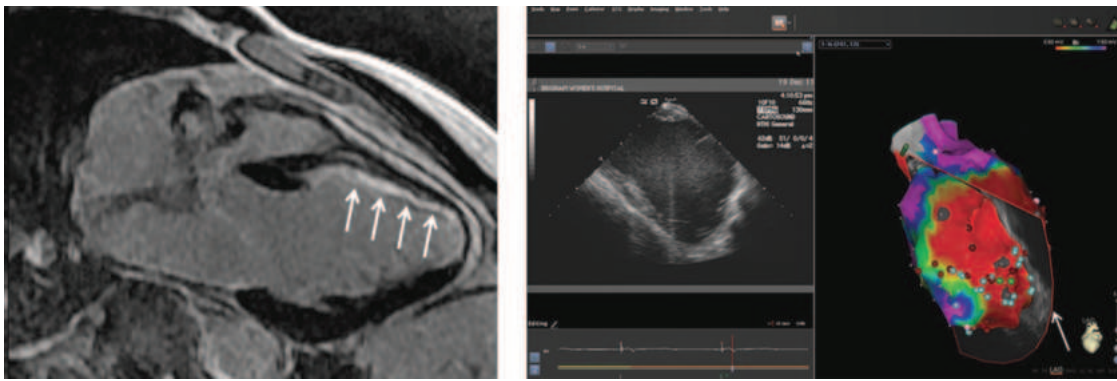


FIGURE 259-5 Imaging studies of the left ventricle (LV) used to assist ablation for ventricular tachycardia (VT). *Left panel* is a magnetic resonance image of a longitudinal section demonstrating thinning of the anterior wall and late gadolinium enhancement in a subendocardial scar (white arrows). The *middle panel* shows a two-dimensional image of the LV in long axis corresponding to the sector through the mid-LV (arrow in figure on right panel) obtained by an intracardiac echocardiography probe positioned in the right ventricle. An electroanatomic three-dimensional map of the LV in the left anterior oblique projection is displayed in the *right panel*. The purple areas depict areas of normal voltage (>1.5 mV). Blue, green, and yellow represent progressively lower voltages, with the red areas indicating scar (<0.5 mV). Channels of viable myocardium with slow conduction within the scar are identified with the light blue dots. Areas of ablation delivered to regions involved in reentrant VT are indicated by maroon dots.

with heart disease. Bradyarrhythmias and negative inotropic effects are the major cardiac adverse effects.

■ CALCIUM CHANNEL BLOCKERS

The nondihydropyridine calcium channel blockers diltiazem and verapamil can be effective for some idiopathic VTs. The risk of proarrhythmia is low, but they have negative inotropic and vasodilatory effects that can aggravate hypotension.

■ SODIUM CHANNEL-BLOCKING AGENTS

Drugs whose major effect is mediated through sodium channel blockade include mexiletine, quinidine, disopyramide, flecainide, and propafenone, which are available for chronic oral therapy. Blockade of the fast inward sodium current has been referred to as a class I antiarrhythmic drug effect. Antiarrhythmic actions are the result of depressing cardiac conduction and membrane excitability. Conduction slowing can be manifest as a prolongation of QRS duration. Lidocaine, quinidine, and procainamide are available as intravenous formulations. Quinidine, disopyramide, and procainamide also have potassium channel-blocking effects that may prolong the QT interval (class III antiarrhythmic drug action), contributing to their antiarrhythmic effect. Quinidine also blocks a particular potassium current, I_{to} , the blockade of which can be important in Brugada syndrome. These agents have potential proarrhythmic effects and, with the possible exception of quinidine, also have negative inotropic effects that may have contributed to the increased mortality observed when some were administered chronically to patients with prior myocardial infarction. Long-term therapy is generally avoided in patients with structural heart disease but may be used to reduce symptomatic arrhythmias in patients with ICDs.

■ POTASSIUM CHANNEL BLOCKING AGENTS

Sotalol and dofetilide block the delayed rectifier potassium channel I_{Kr} , thereby prolonging action potential duration (QT interval) and the cardiac refractory period, known as the class III antiarrhythmic drug effect. Sotalol also has nonselective β -adrenergic-blocking activity. It has been shown to have a modest effect on reducing ICD shocks due to ventricular and atrial arrhythmias. Proarrhythmia due to the polymorphic VT torsade de pointe that is associated with QT prolongation occurs in 3–5% of patients. Both sotalol and dofetilide are excreted via the kidneys, necessitating dose adjustment or avoidance in renal insufficiency. These drugs must be avoided in patients with other risk factors for torsades de pointes, including QT prolongation, other administered medications that prolong the QT interval, hypokalemia, and significant bradycardia.

■ AMIODARONE

Amiodarone blocks multiple cardiac ionic currents and has sympatholytic activity. It is the most effective antiarrhythmic drug for suppressing VAs. It is administered intravenously for life-threatening

arrhythmias. During chronic oral therapy, electrophysiologic effects develop over several days. It is more effective than sotalol in reducing ICD shocks and is often used for VAs in patients with heart disease. Bradyarrhythmias are the major cardiac adverse effect. Ventricular proarrhythmia can occur, but torsades de pointes VT is rare. Noncardiac toxicities are a major problem and contribute to drug discontinuation in at least a third of patients during long-term therapy. Hyper- and hypothyroidism are related to the iodine content of the drug. Pneumonitis or pulmonary fibrosis occurs in ~1% of patients. Photosensitivity is common, and neuropathy and ocular toxicity can occur. Systematic monitoring is recommended during chronic therapy including assessment for thyroid, liver, and pulmonary toxicity. Intravenous administration of amiodarone via a peripheral vein for >24 h can cause severe peripheral thrombophlebitis. Dronedarone has structural similarities to amiodarone but without the iodine moiety. Efficacy for VAs is poor, and dronedarone increases mortality in patients with heart failure, so dronedarone is not typically used for treatment of VAs.

■ IMPLANTABLE CARIOVERTER-DEFIBRILLATORS

ICDs detect sustained VT, largely based on heart rate, and then terminate the arrhythmia. In transvenous devices, VF is terminated by a shock applied between a lead in the right ventricle and the ICD pulse generator. The lead can provide pacing for bradycardia if needed. This transvenous form of ICD has the disadvantages of vascular occlusion, risk of lead fracture, endocarditis in the event of infection, and difficulty with removal. Monomorphic VT can also be terminated by a burst of rapid pacing faster than the VT, known as antitachycardia pacing (ATP) (Fig. 259-6A). If ATP fails or is not a programmed treatment, as is often the case for rapid VT or VF, a shock is delivered (Fig. 259-6B). ICDs can also be subcutaneous or extravascular, without a transvenous lead. The rhythm is also sensed by this lead, in a manner similar to a surface ECG. The lead is placed overlying the left chest with a coil parallel and next to or underneath the sternum. No matter the type of ICD, shocks are uncomfortable and distressing if the patient is conscious, sometimes leading to a posttraumatic stress disorder (PTSD). The most common ICD complication is the delivery of unnecessary therapy (either ATP or shocks) in response to an inappropriately detected rapid supraventricular tachycardia or electrical noise as a result of an ICD lead fracture or electromagnetic interference from an external source. ICDs record and store electrograms from arrhythmia episodes that can be retrieved by interrogation of the ICD, which can be performed remotely and communicated via the internet. This assessment is critical after an ICD shock to determine the arrhythmia diagnosis and exclude unnecessary therapy. Device infection is an important problem long term and occurs in ~1% of patients. This risk may be less for subcutaneous or extravascular implants.

ICDs decrease mortality in patients at risk for sudden death due to structural heart diseases. In all cases, ICDs are recommended only if there is also an expectation for survival of at least a year with acceptable

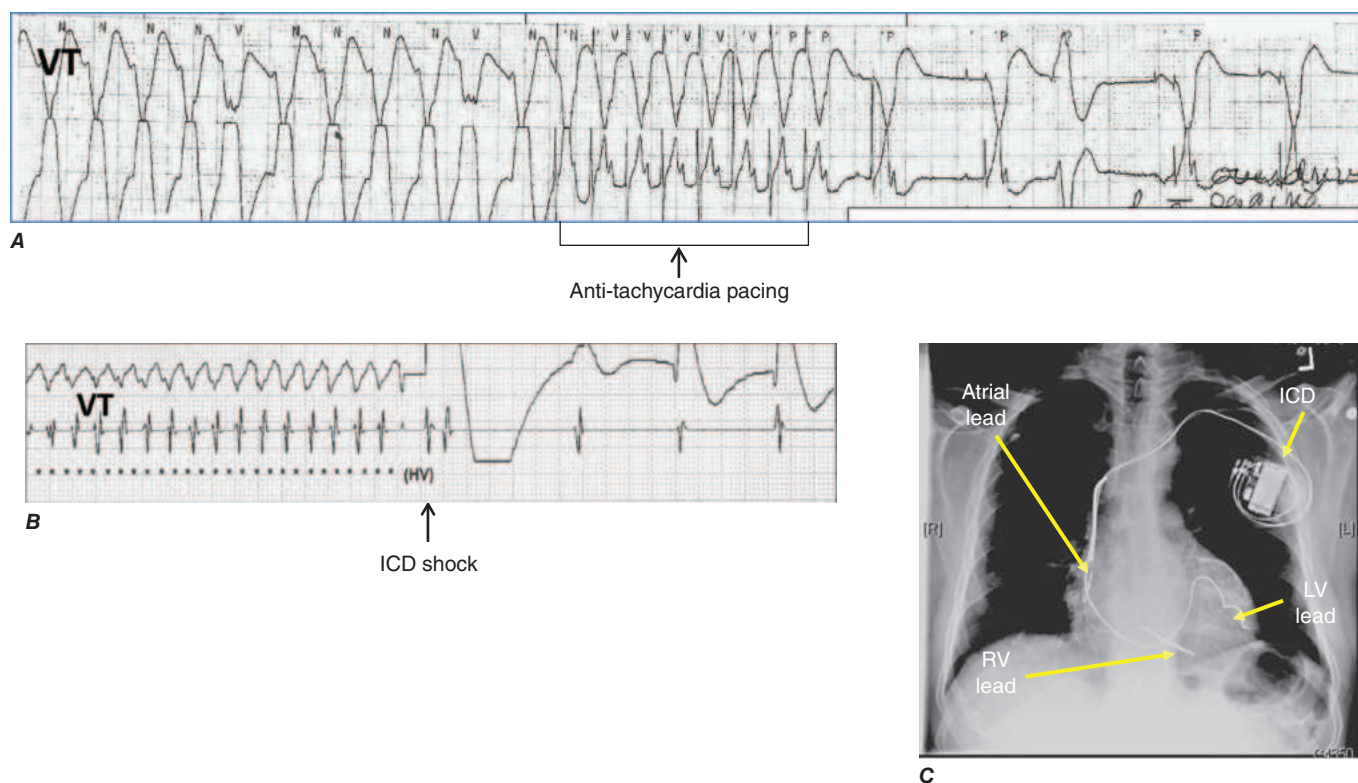


FIGURE 259-6 Implantable cardioverter-defibrillator (ICD) and therapies for ventricular arrhythmias. A. A monomorphic ventricular tachycardia (VT) is terminated by a burst of pacing impulses at a rate faster than VT (antitachycardia pacing). **B.** A rapid VT is converted with a high-voltage shock (arrow). The chest x-ray in the panel **C** shows the components of an ICD capable of biventricular pacing (yellow arrows). ICD generator in the subcutaneous tissue of the left upper chest, pacing leads in the right atrium and the left ventricular (LV) branch of the coronary sinus (LV lead), and a pacing/defibrillating lead in the right ventricle (RV lead) are shown.

functional capacity. The exception is in cases of patients with end-stage heart disease who are awaiting cardiac transplantation outside the hospital or who have left bundle branch block QRS prolongation such that they are likely to have improvement in ventricular function with cardiac resynchronization therapy from a biventricular ICD or conduction system pacing (Fig. 259-6C). In these cases, an ICD may be warranted despite a guarded prognosis. A wearable ICD system with electrodes incorporated into a vest and an external battery pack is also available for short-term use in patients pending a decision regarding a permanent implanted system, or when a permanent system cannot be implanted for other reasons such as an ongoing infection.

Despite prompt termination of VT or VF by an ICD, the occurrence of these arrhythmias predicts subsequent increased mortality and risk of heart failure. Occurrence of VT or VF should therefore prompt assessment for potential causes including worsening heart failure, electrolyte abnormalities, and ischemia. Repeated shocks, even if appropriate, often induce posttraumatic stress disorder. Antiarrhythmic drug therapy, most commonly amiodarone, or catheter ablation is often required for suppression of recurrent arrhythmias. Antiarrhythmic drug therapy can alter the VT rate and the energy required for defibrillation, thereby necessitating programming changes in the ICD's algorithms for detection and therapy.

■ CATHETER ABLATION FOR VT

Catheter ablation is usually performed by applying radiofrequency (RF) current to cause thermal injury by resistive heating of cardiac tissue responsible for the arrhythmia. An electrode catheter with an electroanatomic mapping system is used to map local electrical activity to identify the ventricular myocardium that is causing the arrhythmia, referred to as the arrhythmia substrate. The size and location of the arrhythmia substrate determine the ease and likely effectiveness of the procedure, as well as the potential complications. When the arrhythmia originates from the endocardium, as is most commonly the case, it can be reached from an endovascular approach via a femoral vein or artery. Less commonly, arrhythmias originate from the subepicardium, and percutaneous pericardial puncture, similar to pericardiocentesis,

is required to insert a catheter into the pericardial space for mapping and ablation. In patients with scar-related VT due to prior infarction or cardiomyopathy, ablation typically targets abnormal regions in the scar or region of fibrosis. Because these scars often contain multiple reentry circuits over relatively large regions, extensive areas of ablation can be required, and these areas are often identified as regions of low voltage displayed on electroanatomic reconstructions of the ventricle (Fig. 259-5).

Catheter ablation is often performed in patients with recurrent VAs associated with poor cardiac function, and the procedure-related mortality in this situation is 0.5–3%. Outcomes are better for patients with prior infarction and VT than for patients with nonischemic cardiomyopathies in which the scar locations are more variable and often intramural or subepicardial. Ablation can be lifesaving for patients with very frequent or incessant VT. Methods of delivering ablative energy to intramural areas or areas requiring very extensive ablation are under development. These include needle catheters capable of delivering ablative energy into intramural sources, and bipolar ablation where radiofrequency energy is delivered across two ablation catheters. Stereotactic body radiation therapy (SBRT), classically used for treating thoracic tumors, has been used to direct radiation therapy to a specific portion of the scar substrate to noninvasively ablate VT with encouraging early studies.

Idiopathic VTs and PVCs that occur in the absence of structural heart disease usually originate from a small focus, for which catheter ablation typically has a higher success rate for preventing recurrent arrhythmia. Long-term arrhythmia-free survival in these patients is excellent.

ARRHYTHMIA SURGERY

When antiarrhythmic drug therapy and catheter ablation fail or are not an option, surgical cryoablation, often combined with aneurysmectomy, can be effective therapy for recurrent VT due to prior myocardial infarction and has also been used successfully in a few patients with nonischemic heart disease. Few centers now maintain the expertise for this therapy, though some use this therapy as an adjunct to ventricular assist device implantation.

FURTHER READING

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260 Premature Ventricular Contractions, Nonsustained Ventricular Tachycardia, and Accelerated Idioventricular Rhythm

William H. Sauer, Usha B. Tedrow

Ventricular ectopic beats are very common and may be identified during outpatient or inpatient telemetry monitoring either due to symptoms of palpitations or as an incidental finding. In most cases, ventricular ectopy, presenting as premature ventricular contractions (PVCs), nonsustained ventricular tachycardia (NSVT), and accelerated idioventricular rhythm (AIVR), is asymptomatic and does not require specific treatment. While most commonly benign when presenting in patients with structurally normal hearts and normal electrocardiograms (ECGs), these ventricular arrhythmias can rarely be associated with structural heart disease and a risk of sudden death.

PREMATURE VENTRICULAR CONTRACTIONS AND NONSUSTAINED VENTRICULAR TACHYCARDIA

PVCs are very common and can be due to enhanced automaticity, triggered automaticity, or localized reentry. PVCs are often sensitive to sympathetic stimulation and can be a sign of increased sympathetic tone, myocardial ischemia, hypoxia, electrolyte abnormalities, or underlying heart disease. During myocardial ischemia or in association with other structural heart disease, PVCs can be a harbinger of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF).

The ECG characteristics of the arrhythmia are often suggestive of whether structural heart disease is present. PVCs with smooth uninterrupted contours and sharp QRS deflections may suggest an ectopic focus in relatively normal myocardium, whereas broad notching and slurred QRS deflections may suggest a diseased myocardial substrate. The QRS morphology also suggests the likely site of origin within the ventricle. PVCs that have a dominant S wave in V_1 , referred to as a left bundle branch block–like configuration, originate from the right ventricle or interventricular septum. Those with a dominant R wave in V_1 originate from the left ventricle. A superior frontal plane axis

(negative in II, III, aVF) indicates initial depolarization of the inferior wall (diaphragmatic aspect of the heart), whereas an inferior frontal plane axis (positive in II, III, aVF) indicates an origin in the cranial aspect of the heart. The location of arrhythmia origin often suggests the nature of underlying heart disease. Most common ventricular arrhythmias that are not associated with structural heart disease have a left bundle branch block–like configuration. PVCs with a right bundle branch block configuration are more likely to be associated with structural heart disease. Multiple morphologies of PVCs (multifocal PVCs) are also more likely to indicate structural heart disease or a myopathic disease process. In patients with heart disease, greater frequency and complexity (couplets and NSVT) of these arrhythmias are associated with more severe disease.

PVCs AND NSVT DURING ACUTE ILLNESS

These arrhythmias are often encountered in patients who are being evaluated in the emergency department or who have been hospitalized and are on an ambulatory cardiac monitor. When encountered during acute illness or as a new finding, evaluation should focus on detection and correction of potential aggravating factors and causes, specifically myocardial ischemia, ventricular dysfunction, and electrolyte abnormalities, most commonly hypokalemia. If there is a suspicion of underlying heart disease, then this should be evaluated. Otherwise, asymptomatic PVCs and NSVT in the hospitalized patient do not indicate any specific treatment outside the patient's presenting illness.

PVCs AND NSVT IN PATIENTS WITHOUT HEART DISEASE

Idiopathic ventricular arrhythmias frequently originate from the left or right ventricular outflow tracts near the valve annuli, giving rise to PVCs or VT that have a left bundle branch block–like configuration, with an inferiorly directed frontal plane axis, as discussed below. Other regions that give rise to PVCs in normal hearts include the papillary muscles and fascicular tissue. NSVT from a benign idiopathic source is usually monomorphic, with rates <200 beats/min. NSVT that is very rapid, polymorphic, or with a first beat that occurs prior to the peak of the T wave (“short-coupled”) is uncommon and should prompt concern and careful evaluation for underlying disease or genetic syndromes associated with sudden death.

A family history of sudden death should prompt evaluation for genetic syndromes associated with sudden death, including cardiomyopathy, long QT syndrome, and arrhythmogenic right ventricular cardiomyopathy (ARVC) (see below). Any abnormality on the 12-lead ECG warrants further evaluation. Repolarization abnormalities are seen in a number of genetically determined syndromes associated with sudden death, including the long QT syndrome, Brugada syndrome, ARVC, and hypertrophic cardiomyopathy (Fig. 260-1). Structural abnormalities such as mitral valve prolapse and mitral annular disjunction can be associated with papillary muscle PVCs and sudden death. An echocardiogram is often necessary to assess ventricular function, wall motion abnormalities, and valvular heart disease. Contrast-enhanced cardiac magnetic resonance imaging (MRI) is also useful for this purpose and for the detection of ventricular scarring that is the substrate for sustained VT. Exercise stress testing should be performed in patients with effort-related symptoms and for those at risk for coronary artery disease.

TREATMENT OF IDIOPATHIC ARRHYTHMIAS

For PVCs and NSVT in the absence of structural heart disease or a genetic sudden death syndrome, no specific therapy is needed unless the patient has significant symptoms or evidence that frequent PVCs are depressing ventricular function (see below). Reassurance that the arrhythmia is benign is often sufficient to allow the patient to cope with the symptoms, which will often wax and wane in frequency over years. Avoiding stimulants, such as caffeine and alcohol, is helpful in some patients. If symptoms require treatment, β -adrenergic blockers and nondihydropyridine calcium channel blockers (verapamil and

diltiazem) are sometimes helpful. If these fail, more membrane active antiarrhythmic drugs and catheter ablation are options. The antiarrhythmic agents flecainide, propafenone, mexiletine, and amiodarone can be effective, but the potential for side effects warrants careful consideration prior to prescribing these agents for long-term use. Catheter ablation is effective at suppressing this arrhythmia in ~90% of patients. Failure of ablation is usually due to inability to provoke the arrhythmia for mapping in the electrophysiology laboratory or if the site of origin is near a vital structure, such as the coronary arteries or His-Purkinje system, or is not accessible due to a site of origin deep within the myocardium.

PVCs AND NSVT ASSOCIATED WITH ACUTE CORONARY SYNDROMES

In the peri-infarct period, PVCs and NSVT are common and can be an early manifestation of ischemia and a harbinger of subsequent VF. Treatment with β -adrenergic blockers and correction of hypokalemia and hypomagnesemia reduce the risk of VF. Routine administration of antiarrhythmic drugs such as lidocaine or amiodarone does not reduce mortality and is not indicated for suppression of PVCs or asymptomatic NSVT but may be implemented transiently if an episode of sustained VT or VF occurs, with the goal of reducing the likelihood of a subsequent episode.

Following recovery from acute myocardial infarction (MI), frequent PVCs (typically >10 PVCs/h), repetitive PVCs with couplets, and NSVT are markers for depressed ventricular function and increased mortality, but routine antiarrhythmic drug therapy to suppress these arrhythmias has not been shown to improve mortality. Therefore, amiodarone is an option for treatment of symptomatic arrhythmias in this population when the potential benefit outweighs its potential toxicities. β -Adrenergic blockers reduce sudden death but have limited effect on spontaneous arrhythmias.

For survivors of an acute MI, an implantable cardioverter-defibrillator (ICD) reduces mortality in certain high-risk groups: patients who have survived >40 days after the acute MI and have a left ventricular ejection fraction of <30%, or who have an ejection fraction <35% and have symptomatic heart failure (functional class II or III); and patients >5 days after MI who have a reduced left ventricular ejection fraction, NSVT, and inducible sustained VT or VF on electrophysiologic testing. ICDs do not reduce total mortality when routinely implanted early after MI and have not been demonstrated to improve mortality when implanted early after coronary artery revascularization.

PVCs AND NSVT ASSOCIATED WITH DEPRESSED VENTRICULAR FUNCTION AND HEART FAILURE

PVCs and NSVT are common in patients with depressed ventricular function and heart failure and are markers for disease severity and increased mortality, but antiarrhythmic drug therapy to suppress these arrhythmias has not been shown to improve survival. The use of antiarrhythmic drugs whose major action is blockade of the cardiac sodium channel (flecainide, propafenone, mexiletine, quinidine, and disopyramide) is avoided in patients with structural heart disease because of a risk of proarrhythmia and negative inotropic effects. Amiodarone suppresses ventricular ectopy and reduces sudden death but does not improve overall survival. ICDs are the major therapy to protect against sudden death in patients at high risk and are recommended for those with a left ventricular ejection fraction <35% and New York Heart Association class II or III heart failure, in whom they reduce mortality from 36 to 29% over 5 years.

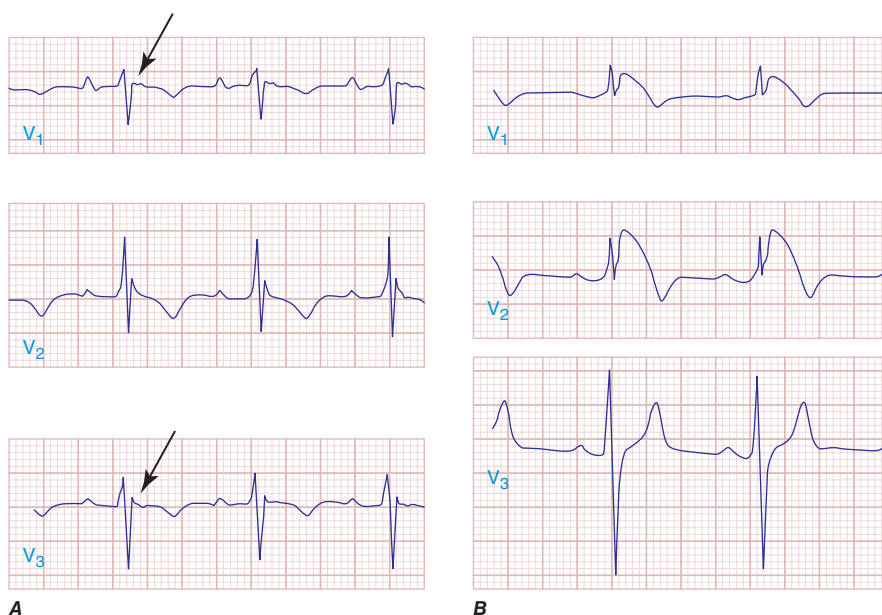


FIGURE 260-1 Electrocardiogram leads depicting Brugada syndrome. Precordial chest leads V₁–V₃ showing typical abnormalities of arrhythmogenic right ventricular cardiomyopathy (ARVC) (**A**) and Brugada syndrome (**B**). In ARVC, there is T inversion and delayed ventricular activation manifest as epsilon waves (arrows). Panel **B** shows ST elevation in V₁ and V₂ typical of the Brugada syndrome.

PVC AND NSVT ASSOCIATED WITH OTHER CARDIAC DISEASES

Ventricular ectopy is associated with increased mortality in patients with hypertrophic cardiomyopathy or with congenital heart disease associated with right or left ventricular dysfunction. In these patients, management is similar to that for patients with ventricular dysfunction. Pharmacologic suppression of the arrhythmia has not been shown to improve mortality. ICDs are indicated for patients considered at high risk for sudden cardiac death.

PVC-INDUCED VENTRICULAR DYSFUNCTION

Very frequent ventricular ectopy and repetitive NSVT can depress ventricular function, possibly through an effect similar to chronic tachycardia or by inducing ventricular dyssynchrony. Depression of ventricular function rarely occurs unless PVCs account for at least 10–20% of total beats over a 24-h period, and only a minority of patients with PVCs will have a reversible cardiomyopathy. Often the PVCs are idiopathic and unifocal, most commonly originating from the outflow tract regions or left ventricular papillary muscles (**Fig. 260-2**), where they can be targeted for ablation.

Other sites of origin such as the mitral and tricuspid valve annuli, right ventricular moderator band, and even the epicardial surface of the heart also occur (**Fig. 260-3**). The factors that can potentially predict development of heart failure and increased risk of adverse outcomes include PVC frequency, characteristics of the PVC morphology, and timing of the PVC coupling interval. In addition, the presence of late gadolinium enhancement on cardiac MRI may suggest the presence of an additional underlying cardiomyopathic process. The degree of expected recovery of ventricular function with PVC suppression is difficult to predict. Even in the setting of known underlying cardiomyopathy, controlling frequent ventricular ectopy can be helpful to improve ejection fraction and improve other factors such as delivery of resynchronization pacing.

ACCELERATED IDIOVENTRICULAR RHYTHMS

Three or more ventricular beats at a rate slower than 100 beats/min are termed an AIVR (**Fig. 260-4**). Automaticity is the likely mechanism, although in some rare cases, a reentrant circuit utilizing diseased

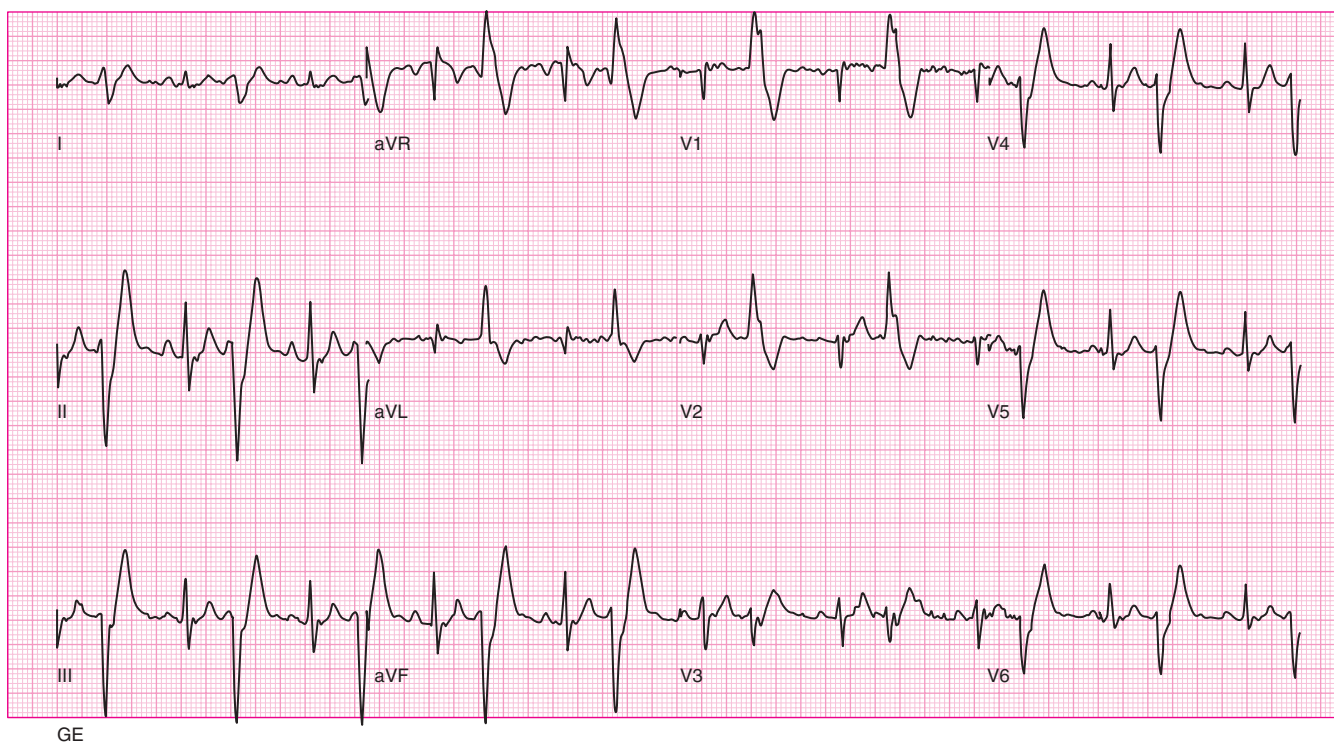


FIGURE 260-2 Ventricular bigeminy with premature ventricular contractions (PVCs) originating from the posteromedial papillary muscle. Twelve-lead electrocardiogram showing normal sinus rhythm with ventricular bigeminy. The PVCs have a right bundle branch block configuration in V_1 with superiorly directed axis. The leads V_4 – V_6 are negative. The configuration is consistent with a PVC origin in the posteromedial papillary muscle of the left ventricle.



FIGURE 260-3 Catheter ablation of premature ventricular contractions (PVCs) from the left ventricular outflow tract. Shown is an electroanatomic map on the left and PVC morphology with superimposed pacing morphology on the right. The left ventricle is seen from the atrial side (posteriorly), and an ablation catheter is seen passing through the aortic valve at the top of the electroanatomic map and contacting the anterolateral portion of the left ventricular outflow tract. Maroon dots are ablation lesions that have been delivered at the site of interest. Pacing from the site of interest generates a QRS complex very similar to the clinical PVC as seen on the right.

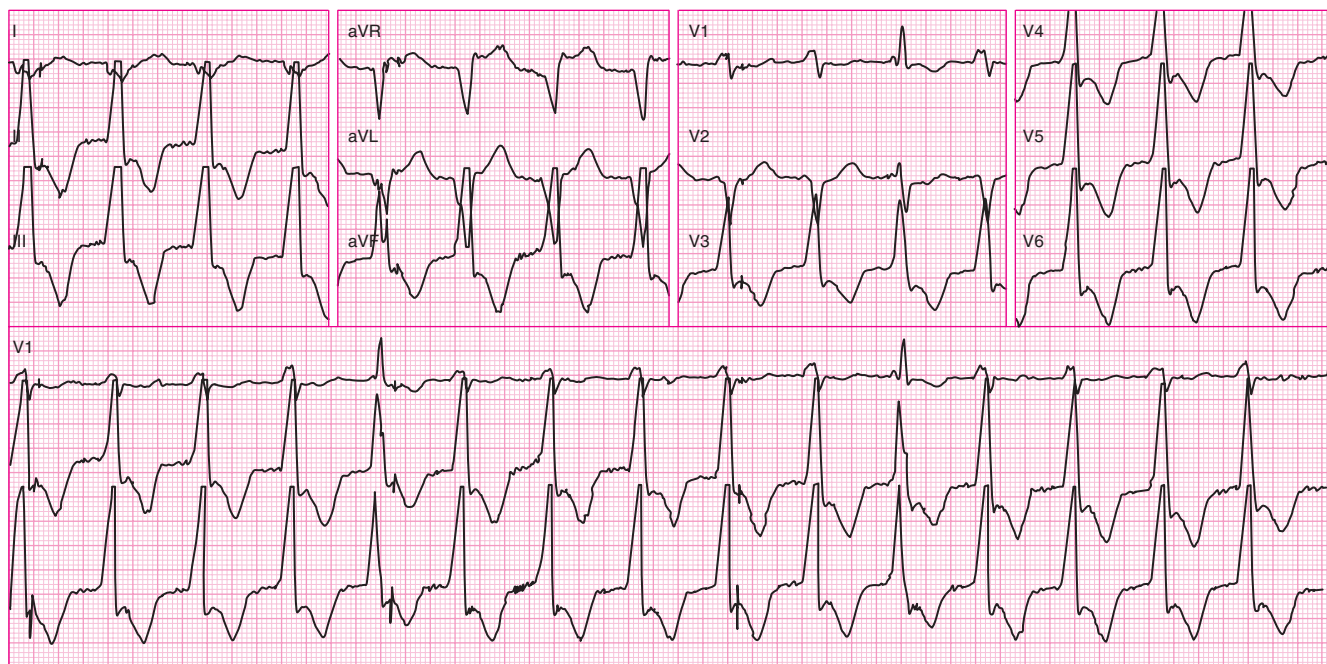


FIGURE 260-4 Accelerated idioventricular rhythm. Shown is an example of a slow regular wide-complex rhythm. Fusion beats are seen on complexes 4 and 10, which are more positive in lead V₁ and narrower than the rest of the beats. These features are consistent with an accelerated idioventricular rhythm.

myocardium can cause AIVR. Idioventricular rhythms are common during acute MI and may emerge during sinus bradycardia. Often, they are not symptomatic, but hemodynamic compromise may occur with the loss of atrioventricular synchrony in susceptible patients. Atropine may be administered to increase the sinus rates if this is a concern. This rhythm is also common in patients with cardiomyopathies or sleep apnea. It can also be idiopathic, often emerging when the sinus rate slows during sleep. Therapy should target any underlying cause and correction of bradycardia. Specific antiarrhythmic therapy for asymptomatic idioventricular rhythm is not necessary.

FUTURE DIRECTIONS

Recently, it has been appreciated that inflammation plays a role in the genesis of PVCs in specific patients with inflammatory cardiomyopathies and even in inherited cardiomyopathies. The roles of early identification of this process and targeted treatment are areas of active research.

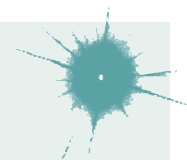
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261

Sustained Ventricular Tachycardia

William H. Sauer, Usha B. Tedrow



Sustained monomorphic ventricular tachycardia (VT) is a ventricular arrhythmia with a wide QRS lasting for at least 30 s or requiring an intervention such as antitachycardia pacing from a defibrillator or a cardioversion for termination. Each QRS complex resembles the others, indicating either a focal site of origin or a repetitive exit from a fixed arrhythmia reentry circuit. In structural heart disease, the arrhythmia substrate is most often an area of patchy replacement fibrosis due to infarction, fibrosis, inflammation, or prior cardiac surgery that creates anatomic or functional reentrant pathways. Less commonly, VT is related to reentry or automaticity in diseased conduction pathways in the Purkinje system. While scar-related reentrant VTs are associated with risk of sudden death, idiopathic VT is a more benign form of VT that occurs in structurally normal hearts and can be due to a focal region of automaticity in the myocardium or reentry involving a portion of the Purkinje system.

The clinical presentation varies depending on the rate of the arrhythmia, underlying cardiac function, and autonomic adaptation in response to the arrhythmia. Rapid VT can produce hypotension that may present as syncope, particularly in patients with significant ventricular dysfunction. In contrast, patients with normal cardiac function might tolerate sustained VT, even presenting with simple palpitations, despite rapid rates. Monomorphic VT that is rapid or associated with structural heart disease may eventually deteriorate to ventricular fibrillation (VF), which may be the initial cardiac rhythm recorded at the time of resuscitation of an out-of-hospital cardiac arrest.

DIAGNOSIS

Sustained monomorphic VT ([Table 261-1](#)) has to be distinguished from other causes of uniform wide QRS tachycardia. These include supraventricular tachycardia with left or right bundle branch block

TABLE 261-1 Sustained Ventricular Arrhythmias**1. Idiopathic ventricular tachycardia (VT) without structural heart disease****A. Outflow tract origin**

- Right ventricular (RV) outflow tract: left bundle branch block pattern in V_1 with inferior axis (tall QRS in inferior leads) and late transition in the precordial leads
- Left ventricular (LV) outflow tract: similar inferiorly directed axis but with early precordial transition with prominent R wave in V_2 – V_3

B. LV fascicular VT: Typical right bundle branch block pattern in V_1 with sharp intrinsicoid deflection and left axis deviation (arising from left posterior fascicle in its most common form)**C. Papillary muscle VT**

- Posteromedial: atypical right bundle branch block pattern in V_1 with monophasic R wave and left axis deviation
- Anterolateral: atypical right bundle branch block pattern in V_1 with positive deflection in lead III and negative deflection in lead I

2. Ischemic cardiomyopathy

- Monomorphic VT is common with prior large myocardial infarction
- Polymorphic VT and ventricular fibrillation (VF) should prompt ischemia evaluation

3. Nonischemic cardiomyopathy

- Fibrotic scars can cause monomorphic VT, especially with sarcoidosis or other inflammatory cardiomyopathies, Chagas' disease, and familial arrhythmogenic cardiomyopathies such as Lamin A/C genetic cardiomyopathy
- Polymorphic VT and VF can also occur independently or related to degeneration of monomorphic VT

4. Arrhythmogenic RV cardiomyopathy

- Monomorphic VT usually of RV origin (left bundle branch morphology in V_1)
- Polymorphic VT and VF can occur independently or related to degeneration of monomorphic VT

5. Repaired tetralogy of Fallot

- Monomorphic VT of RV origin (usually left bundle branch morphology in V_1)

6. Hypertrophic cardiomyopathy

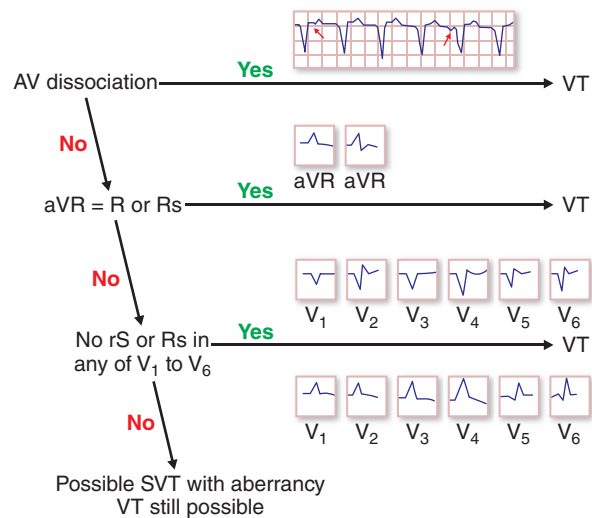
- Polymorphic VT or ventricular fibrillation
- Less commonly, monomorphic VT associated with myocardial scars, particularly apical aneurysms

7. Genetic arrhythmia syndromes

- A. Long QT syndrome**
 - Torsades des pointes VT
- B. Brugada syndrome**
 - Ventricular fibrillation episodes, often nocturnal
- C. Catecholaminergic polymorphic VT**
 - Polymorphic VT or bidirectional VT
- D. Short QT and early repolarization syndromes**
 - Ventricular fibrillation

8. Idiopathic polymorphic VT or ventricular fibrillation

- Usually triggered by recurrent premature ventricular contractions; the most common site of origin is the left posterior fascicle (right bundle branch block/left anterior fascicular block pattern)

VT versus Supraventricular Tachycardia (SVT) with Aberrancy**FIGURE 261-1 Algorithm for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia with aberrancy.** AV, atrioventricular.

ventriculoatrial (VA) dissociation is a reliable marker for VT, provided the atrial rate is slower than the ventricular rate. Sometimes, P waves can be difficult to define, and the VA relationship cannot be assessed in a patient with an ongoing atrial arrhythmia such as atrial fibrillation. A P wave following each QRS does not exclude VT because 1:1 conduction from ventricle to atrium can occur. A monophasic R wave or Rs complex in aVR or concordance from V_1 to V_6 of monophasic R or S waves is also relatively specific for VT (Fig. 261-1). A number of other QRS morphology criteria have also been described, but all have limitations and are not very reliable in patients with severe heart disease. In patients with known bundle branch block, the same QRS morphology during tachycardia as during sinus rhythm suggests supraventricular tachycardia rather than VT, but even this is not absolutely reliable. Patients with reentry involving the bundle branches of the Purkinje system can have a VT morphology that resembles their native QRS in sinus rhythm. An electrophysiologic study is sometimes required for definitive diagnosis. Occasionally, noise and movement artifacts on telemetry recordings can simulate VT, and prompt recognition of this can avoid unnecessary tests and interventions.

TREATMENT AND PROGNOSIS

Initial management follows Advanced Cardiac Life Support (ACLS) guidelines. If hypotension, impaired consciousness, or pulmonary edema is present, QRS synchronous electrical cardioversion should be performed, ideally after sedation if the patient is conscious. For stable tachycardia, a trial of adenosine is reasonable as this may clarify a supraventricular tachycardia with aberrancy. Adenosine should not be used if the patient has a heart transplant or if the wide-complex rhythm is irregular or unstable. Intravenous amiodarone is the drug of choice if heart disease is present. Following restoration of sinus rhythm, hospitalization and evaluation to define underlying heart disease are required. Assessment of cardiac biomarkers for evidence of myocardial infarction (MI) is appropriate, but acute MI is rarely a cause of sustained monomorphic VT. Elevations in troponin or creatine kinase (CK)-MB are more likely to indicate myocardial injury that is secondary to hypotension and ischemia from fixed coronary lesions during the VT rather than an acute coronary event. Subsequent management is determined by the underlying heart disease and frequency of VT. If VT recurs frequently or is incessant, administration of antiarrhythmic medications or catheter ablation may be required to restore stability. More commonly, sustained monomorphic VT occurs as a single episode but with a high risk of recurrence. Implantable cardioverter-defibrillators (ICDs) are warranted for secondary prevention of sudden death in patients who present with sustained VT associated with structural heart disease (Fig. 261-2).

aberrant conduction, supraventricular tachycardias conducted to the ventricles over an accessory pathway, and rapid cardiac pacing, appropriate or inappropriate, in a patient with a ventricular pacemaker or defibrillator. In the presence of known heart disease, VT is the most likely diagnosis of a wide QRS tachycardia, independent of QRS morphology. When left ventricular (LV) function is depressed or there is evidence of structural myocardial disease, scar-related reentry is the most likely cause of sustained monomorphic VT. Scars are suggested by pathologic Q waves on the electrocardiogram (ECG), segmental LV or right ventricular wall motion abnormalities on echocardiogram or nuclear imaging, and areas of delayed gadolinium enhancement during magnetic resonance imaging (MRI).

Hemodynamic stability during the arrhythmia does not help distinguish between VT and other mechanisms of wide-complex tachycardia. A number of ECG criteria have been evaluated to distinguish supraventricular tachycardia with aberrancy from VT. The presence of

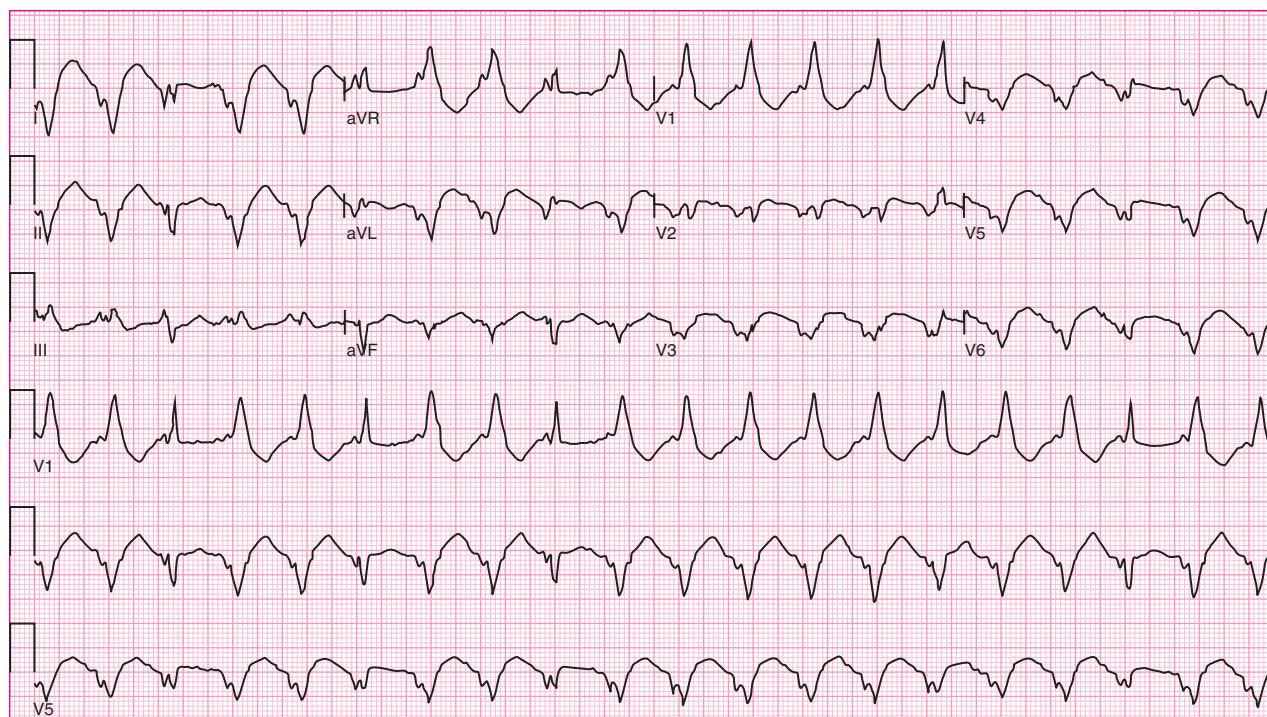


FIGURE 261-2 Monomorphic ventricular tachycardia in a patient with prior myocardial infarction. Shown is a wide-complex tachycardia. Complexes 3, 6, 9, and 18 are narrower and are examples of fusion beats, proving ventriculoatrial (VA) dissociation and proving that this rhythm is in fact ventricular tachycardia.

SUSTAINED MONOMORPHIC VT IN SPECIFIC DISEASES

■ CORONARY ARTERY DISEASE

Patients who present with sustained monomorphic VT associated with coronary artery disease typically have a history of a remote prior large MI. Patients typically present years after the acute infarct with a remodeled ventricle and markedly depressed LV function. Even when there is biomarker evidence of acute MI, a preexisting scar from previous MI should be suspected as the cause of the VT. Infarct scars provide a durable substrate for sustained VT, and up to 70% of patients have a recurrence of the arrhythmia within 2 years. Scar-related reentry is not usually dependent on recurrent acute myocardial ischemia, so coronary revascularization is unlikely to prevent recurrent VT, although it may be appropriate for treatment of angina or other indications. Depressed ventricular function, which is a risk factor for sudden death, is usually present. Implantation of an ICD is clearly indicated for secondary prevention provided that there is a reasonable expectation of survival for 1 year with acceptable functional status. Compared with antiarrhythmic drug therapy, ICDs reduce annual mortality from 12.3 to 8.8% and lower arrhythmic deaths by 50% in patients with hemodynamically significant sustained VT or a history of cardiac arrest. Antiarrhythmic drugs may have some utility for palliation of VT symptoms and prevention of ICD therapies, such as shocks and antitachycardia pacing; however, without an ICD, these drugs do not improve survival.

Following ICD implantation, patients with depressed ejection fraction remain at risk for clinical heart failure, recurrent ischemic events, and recurrent VT, with a 5-year mortality that exceeds 30%. Attention to guideline-directed medical therapy for patients with heart failure and coronary artery disease, including β -adrenergic blocking agents and angiotensin-converting enzyme inhibitors, is important.

ICD therapies, whether shocks or antitachycardia pacing, constitute an adverse event for the patient and are associated with increased rates of heart failure, mortality, and psychological stress. For this reason, recurrent VT episodes in patients with an ICD warrant treatment with medications or catheter ablation. In a randomized study of catheter ablation versus escalated medical therapy (Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs [VANISH]), patients receiving catheter ablation fared better than those receiving increasing doses of antiarrhythmic drugs, in particular, amiodarone.

Another randomized trial (BERLIN VT) examined a preventative versus deferred ablation strategy in patients who had not yet failed an antiarrhythmic drug. This trial was stopped early for futility, with more procedural complications but fewer VT episodes in the catheter ablation group. For this reason, the most recent consensus statement most strongly recommends catheter ablation for patients with ischemic cardiomyopathy failing or intolerant of antiarrhythmic drugs but also allows for consideration of catheter ablation when long-term therapy with an antiarrhythmic drug (such as amiodarone, which has significant long-term toxicities) is not desired ([Table 261-2](#)).

■ NONISCHEMIC DILATED CARDIOMYOPATHY

Sustained monomorphic VT associated with nonischemic cardiomyopathy is usually due to scar-related reentry. The etiology of scar is often unclear, but progressive replacement fibrosis is the likely cause. Patients with nonischemic cardiomyopathy (NICM) have historically been presumed to have a postviral etiology, although increasingly, genetic causes are found in many. Inflammatory etiologies (myocarditis, sarcoidosis) are also increasingly appreciated. On cardiac MRI, scars are detectable as areas of delayed gadolinium enhancement and are more often intramural ([Fig. 261-3](#)) or subepicardial in location as compared with patients with prior MI. Scars that cause VT are often located adjacent to a valve annulus and can occur in either ventricle. Any cardiomyopathic process can cause scars and VT, but cardiac sarcoidosis, Chagas' disease, and cardiomyopathy due to Lamin A/C mutations are particularly associated with monomorphic VT. An ICD is indicated for patients with a history of sustained VT, syncope, or New York Heart Association class II or III heart failure symptoms, with additional drugs or catheter ablation for control of recurrent VT. In addition, for patients with malignant familial arrhythmogenic cardiomyopathies, an ICD may be considered earlier in the clinical course.

Overall, there are fewer studies of catheter ablation for VT in NICM. Reported success rates are lower than VT ablation in ischemic cardiomyopathy in most observational series. Additionally, inability to reproduce the clinical VT at ablation attempts and epicardial and intramural reentry circuits are important causes of failure of endocardial VT ablation in NICM. Imaging with MRI or computed tomography (CT) scans with late contrast administration to define areas of fibrosis can be useful to guide ablation ([Table 261-2](#)).

TABLE 261-2 Summary of Randomized Controlled Studies Assessing Catheter Ablation of Ventricular Tachycardia in Patients with Structural Heart Disease										
STUDY, YEAR	STUDY PERIOD	SAMPLE SIZE		INCLUSION CRITERIA	CONTROL ARM	AGE (years)	MALE (%)	ICM (%)	BASELINE LVEF (%)	FOLLOW-UP (months)
		CA	OC							
SMASH-VT, 2007	2000–2006	64	64	Prior MI, ICD for VF or unstable VT	Medical therapy	67 ± 10	87	100	32 ± 9	22.5 ± 5.5
VTACH, 2010	2002–2006	52	55	Prior MI, LVEF ≤50%, ICD indicated for stable VT	ICD + medical therapy	66 ± 8	93	100	34 ± 9	22.5 ± 9
CALYPSO, 2015	2012–2014	13	14	IHD, ≥1 ICD shock or ≥3 ATP therapies for monomorphic VT in last 6 months	AAD therapy	63 ± NR	93	100	30 ± NR	6
VANISH, 2016	2009–2015	132	127	Prior MI, ICD in situ, ≥1 episode of VT while on a class I/III AAD	Escalation of AAD therapy	69 ± 8	93	100	31 ± 11	27.9 ± 17.1
SMS, 2017	2002–2010	54	57	IHD, LVEF ≤40%, unstable VT	ICD + medical therapy	67 ± 8	84	100	31 ± 7	27.0 ± 13.2
BERLIN-VT, 2020	2015–2018	76	83	Prior MI, LVEF 30–50%, ICD in situ for life-threatening VT	Medical therapy until third ICD shock (then VT ablation)	66 ± 10	87	100	41 ± 6	13.2 ± 9.5
PARTITA, 2022	2012–2021	23	24	Cardiomyopathy, had first ICD shock	Medical therapy	68 ± 9	85	81	32 ± 9	24.2 (8.5–24.4)
SURVIVE-VT, 2022	2010–2017	71	73	Prior MI, sustained VT causing ICD shock or syncope	AAD therapy	70 ± 9	96	100	33 ± 11	23
PAUSE-SCD, 2022	2015–2020	60	61	LVEF <50%, ICD indicated for secondary prevention or inducible monomorphic VT on EPS	ICD + medical therapy	55 (46–64)	81	35	40 (30–49)	31.3 (20.1–40)

Abbreviations: AAD, antiarrhythmic drug; ATP, antitachycardia pacing; BERLIN VT, Preventive Ablation of Ventricular Tachycardia in Patients with Myocardial Infarction; CA, catheter ablation; CALYPSO, Catheter Ablation for Ventricular Tachycardia in Patients with an Implantable Cardioverter Defibrillator; EPS, electrophysiology study; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; OC, other care; PARTITA, Does Timing of VT Ablation Affect Prognosis in Patients with an Implantable Cardioverter-Defibrillator?; PAUSE-SCD, Pan-Asia United States Prevention of Sudden Cardiac Death Catheter Ablation Trial; SMASH VT, Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia; SMS, Substrate Modification Study; SURVIVE-VT, Substrate Ablation Versus Antiarrhythmic Drug Therapy for Symptomatic Ventricular Tachycardia; VANISH, Ventricular Tachycardia Ablation Versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease; VF, ventricular fibrillation; VT, ventricular tachycardia; VTACH, Ventricular Tachycardia Ablation in Coronary Heart Disease.

Source: Reproduced with permission from SA Virk, S Kumar: Catheter ablation of ventricular tachycardia in patients with structural heart disease: A meta-analysis. JACC Clin Electrophysiol 9: 255; 2023.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare genetic disorder most commonly due to mutations in genes encoding for cardiac desmosomal proteins; however, it is increasingly appreciated

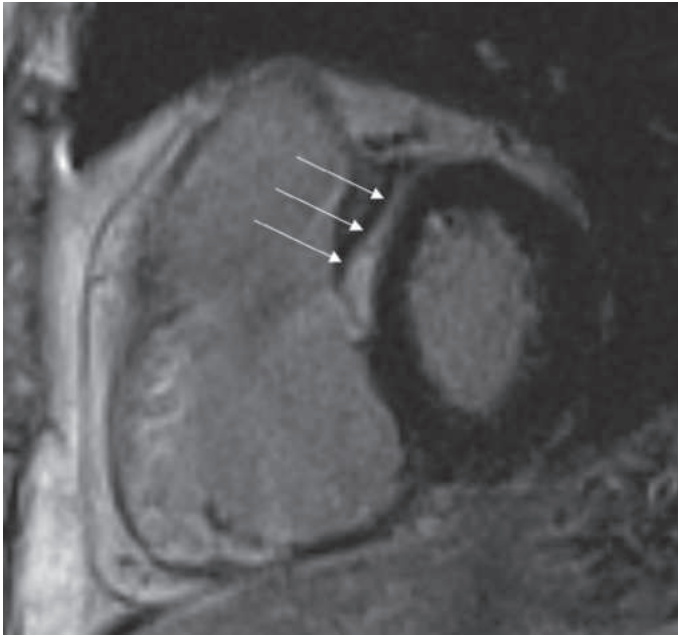


FIGURE 261-3 Cardiac magnetic resonance image (MRI). Shown is an MRI of the heart with the right ventricle on the left and the left ventricle on the right. Between the ventricles (arrows) is a stripe of late gadolinium enhancement, indicating midmyocardial fibrosis in the interventricular septum. This type of scar pattern is often seen in patients with nonischemic cardiomyopathies and ventricular tachycardia.

that other cardiomyopathic processes may produce a similar phenotype. Approximately 50% of patients have a familial transmission with autosomal dominant inheritance. A less common, autosomal recessive form is classically associated with cardiocutaneous syndromes that include Naxos disease and Carvajal syndrome. The former is most commonly related to mutations in plakophilin-2 and plakoglobin, while the latter is most commonly due to a mutation in desmoplakin. Patients are typically diagnosed between the second and fifth decades with palpitations, syncope, or cardiac arrest owing to sustained monomorphic VT, although polymorphic VT can also occur. Fibrosis and fibrofatty replacement most commonly involve the right ventricular myocardium and provide the substrate for reentrant VT that usually has a left bundle branch block-like configuration in ECG lead V₁, consistent with the right ventricular origin, and can resemble idiopathic VT. The sinus rhythm ECG suggests the disease in >85% of patients, most often showing T-wave inversions in V₁–V₃. Delayed activation of the right ventricle may cause a widened QRS (>110 ms) in the right precordial leads (V₁–V₃) and a prolonged S-wave upstroke in those leads and, occasionally, a notched deflection at the end of the QRS known as an epsilon wave. Cardiac imaging may show right ventricular enlargement or areas of abnormal motion or reveal areas of scar on contrast-enhanced MRI.

LV involvement can occur and can occasionally precede manifest right ventricular disease. Clinical heart failure is rare except in late stages, and survival to advanced age can be anticipated provided that VT can be controlled. An ICD is recommended. When VT is exercise induced, it may respond to β-adrenergic blockers and limiting exercise. Sotalol, flecainide, and amiodarone have been used to reduce ventricular arrhythmias. Catheter ablation prevents or reduces VT episodes in 70% of patients, but epicardial mapping and ablation are often required.

ADULT CONGENITAL HEART DISEASE

Among all patients with adult congenital heart disease (ACHD), sustained monomorphic VT is quite rare. However, the most common substrate for sustained VT is seen in those with repairs of a ventricular

septal defect, in particular tetralogy of Fallot (TOF). The prevalence of VT after TOF repair is estimated to be 3–14%, and risk of sudden cardiac death may reach as high as 1% per year in adulthood by the fourth or fifth decade of life. The greatest risk for ventricular arrhythmias is posed via two potential mechanisms: (1) those who have undergone repair involving a ventriculotomy and (2) those with long-standing hemodynamic overload causing ventricular dysfunction and/or hypertrophy independent of surgical incisions.

Monomorphic VT in TOF most commonly occurs in stereotyped circuits due to reentry around areas of surgically created scar in the right ventricle. Factors associated with VT risk include age >5 years at the time of repair, high-grade ventricular ectopy, inducible VT on an electrophysiologic study, abnormal right ventricular hemodynamics, and sinus rhythm QRS duration >180 ms. An ICD is usually warranted for patients who have a spontaneous episode of VT, but ICDs are also considered for patients with multiple risk factors. Catheter ablation or antiarrhythmic drug therapy is used to control recurrent episodes.

BUNDLE BRANCH REENTRY VT

Reentry through the Purkinje system occurs in ~5% of patients with monomorphic VT in the presence of structural heart disease. The reentry circuit typically revolves retrograde via the left bundle and anterograde down the right bundle, thereby producing VT that has a left bundle branch block configuration. The VT QRS morphology may closely resemble the QRS morphology in sinus rhythm. Catheter ablation of the right bundle branch abolishes this VT. Bundle branch reentry is usually associated with severe underlying heart disease. Other scar-related VTs are often present and often require additional therapy.

IDIOPATHIC MONOMORPHIC VT

Idiopathic VT in patients without structural heart disease usually presents with palpitations, lightheadedness, and, rarely, syncope. Episodes can be provoked either by sympathetic stimulation or acute withdrawal of sympathetic tone, as in the immediate postexercise period. The QRS morphology of the arrhythmia suggests the diagnosis (see below). The sinus rhythm ECG is normal. Family history suggests no familial cardiomyopathy or sudden death. Cardiac imaging, including echocardiography and cardiac MRI, shows normal ventricular function and no evidence of ventricular scar. Occasionally, a patient with structural heart disease is found to have concomitant idiopathic VT unrelated to

the structural disease, in which case, the underlying disease should be treated as per the guidelines, separate from the VT. Repeated bursts of nonsustained VT, which may occur incessantly, are known as repetitive monomorphic VT and can cause a tachycardia-induced cardiomyopathy with depressed ventricular function that recovers after suppression of the arrhythmia. Sudden death in isolated idiopathic VT is rare, and an ICD is not recommended.

Outflow tract VTs originate from a focus near the pulmonic or aortic valve annuli, usually with features consistent with triggered automaticity. The arrhythmia may present with sustained VT, nonsustained VT, or premature ventricular contractions (PVCs). Most originate in the right ventricular outflow tract, which gives rise to VT that has a left bundle branch block configuration in V_1 and an axis that is directed inferiorly, with tall R waves in II, III, and aVF. Idiopathic VT can also arise in the LV outflow tract or in sleeves of myocardium that extend along the aortic root. LV origin is suspected when lead V_1 or V_2 has prominent R waves. Although this typical outflow tract QRS morphology favors idiopathic VT, some cardiomyopathies, notably ARVC, can cause PVCs or VT from this region. Excluding these diseases is an initial focus of evaluation (Fig. 261-4).

LV fascicular VT, sometimes referred to as Belhassen's VT or verapamil-sensitive VT, is the second most common form of idiopathic VT after outflow tract VTs. It often presents with sustained VT that has a right bundle branch block–like configuration and is negative in the inferior leads. It is often exercise induced and occurs more often in men than women. The mechanism was originally thought to be focal but has been demonstrated to be due to a small reentry circuit in or near the septal ramifications of the LV Purkinje system. There can be an LV false tendon associated with this rhythm. Despite its reentrant nature, the course of this type of VT is typically benign.

Other sites of origin for idiopathic VT exist, including papillary muscles, mitral and tricuspid valve annuli, and the moderator band in the right ventricle. Even focal sites from the epicardial surface have been described. The presence of VT from these more unusual sites should prompt even more careful assessment for structural heart disease.

MANAGEMENT OF IDIOPATHIC VT

Treatment is required for symptoms or when frequent or incessant arrhythmias depress ventricular function. Symptoms can be controlled with medications including beta blockers, calcium channel blockers,

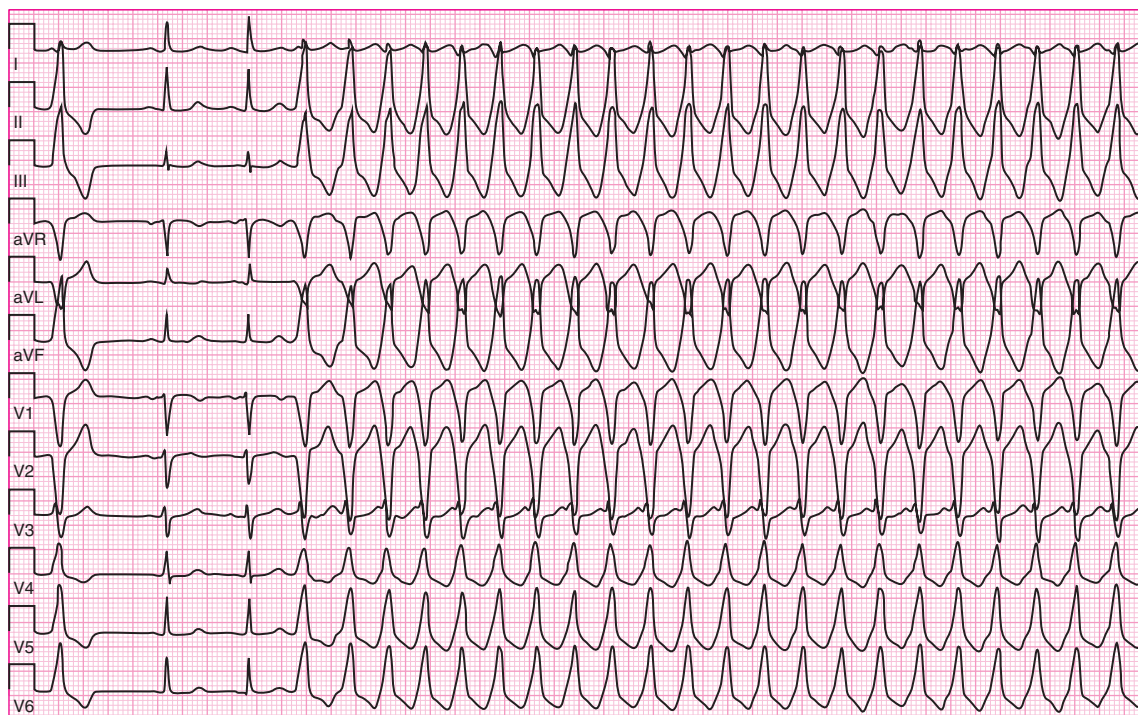


FIGURE 261-4 Idiopathic monomorphic ventricular tachycardia (VT). This is a 12-lead electrocardiogram showing the onset of idiopathic VT in a young patient without structural heart disease. The VT has a left bundle branch block configuration in V_1 and an inferiorly directed axis consistent with an outflow tract origin. Note that the narrow (normal sinus) beats have a normal QRS configuration, consistent with the patient's lack of structural heart disease.

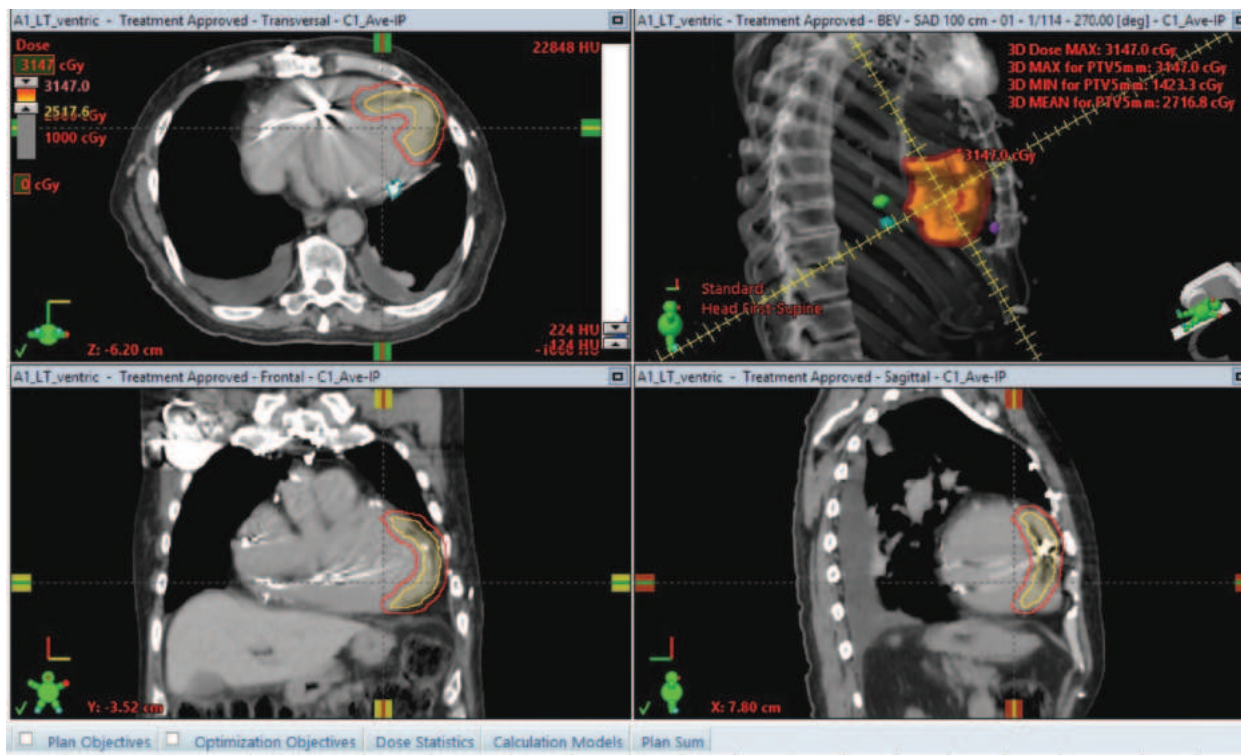


FIGURE 261-5 Stereotactic body radiation therapy. Shown is a planning computed tomography scan for noninvasive cardiac ablation delivered with stereotactic radiation. The region of interest is determined by analysis of presenting arrhythmias, underlying structural heart disease, and proximity to adjacent structures such as coronary arteries, the phrenic nerve, and the gastrointestinal tract. Radiation is delivered to the chosen treatment volume in order to create conduction block in the culprit scar region.

and sodium channel blockers such as flecainide. Although flecainide is not typically recommended in patients with structural heart disease, it has been used successfully to resolve tachycardia-induced cardiomyopathy in the setting of idiopathic PVCs and VT in patients with a normal underlying ECG and no fibrosis evident on cardiac MRI. Catheter ablation is also indicated for control of symptoms, has an overall success rate of 80%, and is recommended for those with symptomatic VT in whom medications are ineffective or not preferred by the patient. Efficacy and risks of catheter ablation vary with the specific site of origin of the VT, being most favorable for arrhythmias originating in the right ventricular outflow tract. Failure of ablation is most often due to inability to initiate the arrhythmia for mapping in the electrophysiology laboratory.

LV interfascicular VT can be terminated by intravenous administration of verapamil, although chronic therapy with oral verapamil is not always effective. Catheter ablation is recommended if β -adrenergic blockers or calcium channel blockers are ineffective or not desired.

FUTURE DIRECTIONS

Treatment of monomorphic VT, especially in the setting of structural heart disease, is an important cause of morbidity and mortality. Limitations of current therapies include toxicities of antiarrhythmic drugs and inability to successfully perform catheter ablation of the substrate for arrhythmias. Advances in imaging and intracardiac mapping techniques are likely to improve success rates over time. In addition, the inability of ablative energy to reach deep intramural substrates is a current limitation. Innovations in delivery of ablative energy, including bipolar ablation, needle catheter ablation, and electroporation, are ongoing. In addition, noninvasive ablation is a promising area of investigation. Proton beam or stereotactic radiation can be used to target VTs identified by advanced cardiac imaging or by a multielectrode ECG vest. Early multicenter studies suggest durable control of VT with noninvasive ablation (Fig. 261-5).

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262

Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

William H. Sauer, Usha B. Tedrow

POLYMORPHIC VENTRICULAR TACHYCARDIA

Sustained polymorphic ventricular tachycardia (VT) has a continuously changing QRS configuration from beat to beat, indicating a continually changing ventricular activation sequence. However, unlike sustained monomorphic VT, polymorphic VT does not necessarily indicate a fixed structural abnormality or focus of automaticity. Reentry can occur with variable reentrant paths, spiral wave reentry, and multiple automatic foci as potential mechanisms. This type of reentry can occur

near fibrotic areas of myocardium, potentiated by proximity to damaged Purkinje cells or ventricular hypertrophy. Abnormal transmural dispersion of repolarization can occur in the setting of channelopathies or antiarrhythmic drugs in the absence of structural heart disease. Sustained polymorphic VT usually degenerates into ventricular fibrillation (VF). Polymorphic VT is typically seen in association with acute myocardial infarction or ischemia (MI), ventricular hypertrophy, and a number of genetic mutations that affect cardiac ion channels.

POLYMORPHIC VT ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION/ISCHEMIA

Acute MI or ischemia is a common cause of polymorphic VT and should be the initial consideration in management. Approximately 10% of patients with acute MI develop VT that degenerates to VF, likely related to reentry through the infarct border zone. The risk is greatest in the first hour of acute MI. More rarely, surviving Purkinje cells with automaticity can initiate polymorphic VT. Following defibrillation as per the Advanced Cardiac Life Support (ACLS) guidelines, management is as for acute MI. β -Adrenergic blockers, correction of electrolyte abnormalities, and prompt myocardial reperfusion are required. Repeated episodes of polymorphic VT may suggest ongoing MI and warrant assessment of adequacy of myocardial reperfusion. Polymorphic VT and VF that occur within the first 48 h of acute MI are associated with greater in-hospital mortality, but patients who survive past hospital discharge are not at increased risk for arrhythmic sudden death. Long-term therapy for postinfarct ventricular arrhythmia is determined by residual left ventricular (LV) function, with an implantable cardioverter defibrillator (ICD) indicated for persistent severe LV dysfunction (LV ejection fraction <35%).

REPOLARIZATION ABNORMALITIES AND GENETIC ARRHYTHMIA SYNDROMES

■ ACQUIRED LONG QT SYNDROME

Abnormal prolongation of the QT interval is associated with the polymorphic VT torsades des pointes. The VT often has a characteristic

initiation sequence of a premature ventricular beat that induces a pause, followed by a sinus beat that has a longer QT interval and interruption of the T wave by the premature ventricular contraction (PVC) that is the first beat of the polymorphic VT (Fig. 262-1). This characteristic initiation is termed *pause-dependent*. Causes of QT prolongation include electrolyte abnormalities, bradycardia, and a number of medications that block repolarizing potassium currents, notably the antiarrhythmic drugs sotalol, dofetilide, and ibutilide, but also a number of other medications used for noncardiac diseases, including erythromycin, pentamidine, haloperidol, phenothiazines, and methadone. Individual susceptibility may be related to genetic polymorphisms or mutations that influence repolarization. The website crediblemeds.org is an excellent resource for the clinician to determine whether a given medication has been reported to prolong the QT interval.

Patients typically present with near-syncope, syncope, or cardiac arrest. Sustained episodes degenerate to VF requiring defibrillation. PVCs and nonsustained VT often precede episodes of sustained VT. Intravenous administration of 1–2 g of magnesium sulphate usually suppresses recurrent episodes. If magnesium alone is ineffective, increasing heart rate with isoproterenol infusion or pacing, to a rate of 100–120 depolarizations/min as required to suppress PVCs, usually suppresses VT recurrences. These maneuvers allow time for correction of associated electrolyte disturbance (hypokalemia and hypocalcemia) and bradycardia and removal of any causative drugs (Table 262-1). Drug interactions that elevate levels of the offending agent are often a precipitating factor. Patients who experience a polymorphic VT induced by QT prolongation should be considered to have a susceptibility to the arrhythmia and should avoid all future exposure to medications known to prolong the QT interval.

■ CONGENITAL LONG QT SYNDROME

The congenital long QT syndrome (LQTS) is caused by mutations in genes coding for cardiac ion channels responsible for ventricular repolarization. The corrected QT (QTc) is typically prolonged to >440 ms in men and 460 ms in women. Symptoms are due to torsades des pointes VT. Several forms of congenital LQTS have been identified, but three groups of mutations that lead to LQTS-1, LQTS-2, and LQTS-3

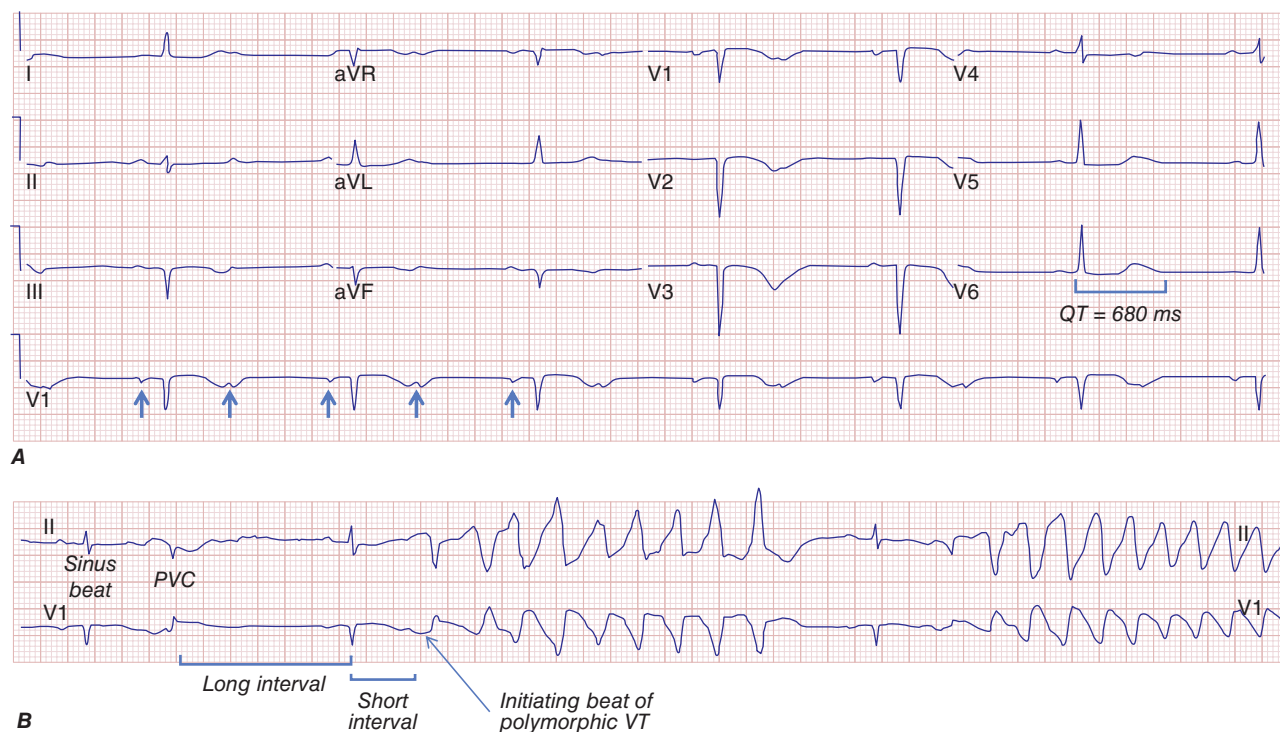


FIGURE 262-1 Torsades des pointes ventricular tachycardia (VT) in a patient with bradycardia and marked QT prolongation. **A.** Twelve-lead electrocardiogram showing 2:1 atrioventricular block (P waves marked by blue arrows) with a heart rate of 40 beats/min and QT interval of 680 ms and corrected QT of 550 ms. **B.** The bottom panel shows a telemetry rhythm strip with periods of self-limiting torsades des pointes polymorphic VT. Following a normally conducted sinus beat, a premature ventricular contraction (PVC) causes a compensatory pause, leading to a long RR interval. A PVC after the next sinus beat initiates VT. This is the classic pause-dependent mode of initiation of torsades des pointes VT with long-short intervals.

TABLE 262-1 Causes of QT Prolongation and Torsades des Pointes

1. Congenital long QT syndromes
 - Long QT syndrome type 1: Reduced repolarizing current I_{Ks} due to mutation in *KCNQ1* gene
 - Long QT syndrome type 2: Reduced repolarizing current I_{Kr} due to mutation in *KCNH2* gene
 - Long QT syndrome type 3: Delayed inactivation of the I_{Na} due to mutations in *SCN5A* gene
 - Others: Several other types of long QT syndromes have been described; long QT syndrome types 1, 2, and 3 account for 80–90% of cases
2. Electrolyte abnormalities: Hypokalemia, hypomagnesemia, hypocalcemia
3. Drug-induced acquired prolongation of QT interval
 - Antiarrhythmic drugs
 - Class IA: Quinidine, disopyramide, procainamide
 - Class III: Sotalol, dronedarone, ranolazine, amiodarone, ibutilide, dofetilide
 - Antibiotics
 - Macrolides: Erythromycin, clarithromycin, azithromycin
 - Fluoroquinolones: Levofloxacin, moxifloxacin
 - Trimethoprim-sulfamethoxazole
 - Clindamycin
 - Pentamidine
 - Chloroquine
 - Antifungals: Ketoconazole, itraconazole
 - Antivirals: Amantadine
 - Antipsychotics
 - Haloperidol, phenothiazines, thioridazine, trifluoperazine, sertindole, zimelidine, ziprasidone
 - Tricyclic and tetracyclic antidepressants
 - Antihistamines (histamine 1-receptor antagonists)
 - Astemizole, diphenhydramine, hydroxyzine
 - Other drugs
 - Citrate (massive blood transfusions)
 - Cocaine
 - Methadone
 - Hydroxychloroquine
4. Cardiac conditions
 - Myocardial ischemia and infarction
 - Myocarditis
 - Marked bradycardia
 - Stress cardiomyopathy
5. Endocrine disorders
 - Hypothyroidism
 - Hyperparathyroidism
 - Pheochromocytoma
 - Hyperaldosteronism
6. Intracranial disorders
 - Subarachnoid hemorrhage
 - Thalamic hematoma
 - Cerebrovascular accident
 - Encephalitis
 - Head injury
7. Nutritional disorders
 - Anorexia nervosa
 - Starvation
 - Liquid protein diets
 - Gastroplasty and ileojejunal bypass
 - Celiac disease

syndromes account for 90% of cases. The most frequently encountered mutations (LQTS-1 and LQTS-2) are due to abnormalities of potassium channels, but mutations affecting the sodium channel (LQTS-3) and calcium channels have also been described.

Typical presentation is with syncope or cardiac arrest, usually during childhood. In LQTS-1, episodes tend to occur during exertion,

particularly swimming. In LQTS-2, sudden auditory stimuli or emotional upset predisposes to events. In LQTS-3, sudden death tends to occur during sleep. Asymptomatic patients may be discovered in the course of family screening or on a routine electrocardiogram (ECG). Genotyping can be helpful for family screening and to provide reassurance regarding the diagnosis. Correlations of genotype with risk and response to therapy are beginning to emerge. In most patients with LQTS-1 or LQTS-2, adequate doses of beta-blocker therapy (the non-selective agents nadolol and propranolol are favored) are sufficient protection from arrhythmia episodes. Markers of increased risk include QTc interval exceeding 500 ms, female gender, and a history of syncope or cardiac arrest. Recurrent syncope despite beta-blocker therapy or a high-risk profile merits consideration of an ICD. Avoidance of QT-prolonging drugs is critical for all patients with LQTS, including those who are genotype positive but have normal QT intervals.

■ SHORT QT SYNDROME

Short QT syndrome is very rare compared to LQTS. The QTc is <360 ms and usually <300 ms. The genetic abnormality causes a gain of function of the potassium channel (I_{Kr}) or reduced inward depolarizing currents. The abnormality is associated with atrial fibrillation, polymorphic VT, and sudden death.

■ BRUGADA SYNDROME

Brugada syndrome is a rare syndrome characterized by >0.2 mV of ST-segment elevation with a coved ST segment and negative T wave in more than one anterior precordial lead (V_1 – V_3) (see Fig. 260-1) and episodes of syncope or cardiac arrest due to polymorphic VT in the absence of structural heart disease. The term *Brugada syndrome* is distinguished from *Brugada pattern* observed in asymptomatic individuals with the characteristic ECG findings, similar to how Wolff-Parkinson-White syndrome is distinguished from the Wolff-Parkinson-White pattern. Cardiac arrest may occur during sleep or be provoked by febrile illness. The mechanism of the ventricular arrhythmias associated with Brugada syndrome are related to the dispersion of repolarization across the ventricular wall with epicardial and M cells that are more affected than endocardial cells. The characteristic coved ST segment in the anterior precordial leads is a consequence of this difference in transmembrane action potentials localized to the right ventricular outflow tract. This regionalized substrate is apparent with epicardial mapping and allows for ablation as a potential treatment option for patients with recurrent VT/VF despite pharmacologic therapy.

Males are more commonly affected than females and men are much more likely to have Brugada pattern on ECG compared to women. In cases where there is a family history, Brugada syndrome demonstrates an autosomal dominant inheritance pattern with variable penetrance. Mutations involving cardiac sodium channels (*SCN5A*, *SCN1B*, and *SCN10A*) are identified in ~25% of cases. There are non-sodium channel genes that have also been described including loss-of-function mutations in calcium and gain-of-function mutations in potassium channel component genes affecting the transient outward current (I_o). Structural and trafficking proteins have also been implicated in Brugada syndrome, revealing a higher level of complexity compared to other monogenetic arrhythmia substrates.

Distinction from patients with similar ST elevation owing to LV hypertrophy, pericarditis, myocardial ischemia or MI hyperkalemia, hypothermia, right bundle branch block, and arrhythmogenic right ventricular cardiomyopathy is often difficult. Furthermore, the characteristic ST-segment elevation can wax and wane over time and may become pronounced during acute illness and fever or with changes in autonomic tone. Administration of the sodium channel-blocking drugs flecainide, ajmaline, or procainamide can augment or unmask ST elevation in affected individuals. An ICD is indicated for individuals who have had unexplained syncope or have been resuscitated from cardiac arrest. Patients with Brugada syndrome must avoid drugs known to affect sodium channels including cocaine, cannabis, some sodium channel antiepileptic agents, and other psychotropic medications. Quinidine and catheter ablation of abnormal regions in the epicardial right ventricular outflow tract have been used successfully to suppress frequent episodes of VT.

■ EARLY REPOLARIZATION SYNDROME

Patients resuscitated from VF who have no structural heart disease or other identified abnormality have a higher prevalence of J-point elevation with notching in the terminal QRS. A family history of sudden death is present in some patients, suggesting a potential genetic basis. J-point elevation is also seen in some patients with the Brugada syndrome and is associated with a higher risk of arrhythmias. An ICD is recommended for those who have had prior cardiac arrest. It should be noted that J-point elevation is commonly seen as a normal variant in patients without arrhythmias, and in the absence of specific symptoms, the clinical relevance is not known.

■ CATECHOLAMINERGIC POLYMORPHIC VT

This rare familial syndrome is due to mutations in the cardiac ryanodine receptor and, less commonly, the sarcoplasmic calcium binding protein calsequestrin 2. These mutations result in abnormal sarcoplasmic calcium handling and polymorphic ventricular arrhythmias that resemble those seen with digitalis toxicity. The VT is polymorphic or has a characteristic alternating QRS morphology termed bidirectional VT. Patients usually present during childhood with exercise or emotion-induced palpitations, syncope, or cardiac arrest. β -Adrenergic blockers (e.g., nadolol and propranolol) and an ICD are usually recommended. Verapamil, flecainide, or surgical left cardiac sympathetic denervation reduces or prevents recurrent VT in some patients. The use of ICDs is controversial because of the fear that an ICD shock could initiate a vicious cycle of adrenergic output and escalated ventricular arrhythmias, leading to death.

■ HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder, occurring in 1 in 500 individuals, and is a prominent cause of sudden death before the age of 35 years. Sudden death can be due to polymorphic VT/VF. Rarely, sustained monomorphic VT occurs related to areas of ventricular scar, most commonly in patients who develop an apical aneurysm. Risk factors for sudden death in this disease include young age, nonsustained VT, failure of blood pressure to increase during exercise, recent (within 6 months) syncope, ventricular wall thickness >3 cm, and possibly the severity of LV outflow obstruction. An ICD is generally indicated for high-risk subjects, but the specific risk profile warranting an ICD continues to

be debated. Surgical myectomy, performed to relieve outflow obstruction, has been associated with a sudden death rate of $<1\%$ per year. The reported annual rate of sustained VT or sudden death after transcatheter ethanol septal ablation done to relieve outflow obstruction has been reported to range between 1 and 5%.

■ GENETIC DILATED CARDIOMYOPATHIES

Genetic dilated cardiomyopathies account for 30–40% of cases of nonischemic dilated cardiomyopathies. Some are associated with muscular dystrophy. Autosomal dominant, recessive, X-linked, and mitochondrial inheritance patterns are recognized. Mutations in genes coding for structural proteins of the nuclear lamina (Lamin A/C) and the *SCN5A* gene are particularly associated with conduction system disease and ventricular arrhythmias. Patients can experience polymorphic VT and cardiac arrest or develop areas of scar causing sustained monomorphic VT. ICDs are recommended for those who have had a sustained VT, are at high risk due to significantly depressed ventricular function (LV ejection fraction $<35\%$ and associated with heart failure), or have a malignant family history of sudden death.

■ VENTRICULAR FIBRILLATION

VF is characterized by disordered electrical ventricular activation without identifiable QRS complexes (Fig. 262-2). Spiral wave reentry and multiple circulating reentry wavefronts are possible mechanisms. Sustained polymorphic or monomorphic VT that degenerates to VF is a common cause of out-of-hospital cardiac arrest. Treatment follows ACLS guidelines with defibrillation to restore sinus rhythm. If resuscitation is successful, further evaluation is performed to identify and treat underlying heart disease and potential causes of the arrhythmia, including the possibility that monomorphic or polymorphic VT could have initiated VF. If a transient reversible cause such as acute MI is not identified, therapy to reduce the risk of sudden death with an ICD is often warranted.

FUTURE DIRECTIONS

The role for catheter ablation in polymorphic VT and VF is rapidly evolving, with some investigators making use of simultaneous electrical recordings from basket catheters to define critical sites for the arrhythmia and correlating these with detailed cardiac imaging to identify typical vulnerable sites for ablation.



FIGURE 262-2 Fascicular ectopy triggering ventricular fibrillation. Shown is a multilead monitor from a patient with recent inferoposterior myocardial infarction and surgical revascularization. Purkinje fibers can often survive acute infarction due to greater cellular glycogen stores and oxygenation from the left ventricular cavity. Upon revascularization, these now surviving but poorly coupled Purkinje fibers can trigger premature ventricular contractions and ventricular fibrillation as shown in this strip.

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263 Electrical Storm and Incessant Ventricular Tachycardia

William H. Sauer, Usha B. Tedrow

ELECTRICAL STORM

Electrical storm or ventricular tachycardia (VT) storm refers to the occurrence of three or more episodes of VT or ventricular fibrillation (VF) within 24 h requiring intervention for termination. Although this disorder is uncommon in the general population, it is of great concern to internists because of its rapid course leading to patient death in the absence of treatment. Therefore, prompt recognition and therapeutic intervention are required. Electrical storms occur in 4% of patients with a primary prevention implantable cardioverter-defibrillator (ICD) but in as many as 20% of patients with a history of known VT or resuscitated sudden death. Catheter ablation, antiarrhythmic drug therapy, and other adjunctive therapies in electrical storms can be life-saving.

INCESSANT VT

VT is designated incessant when VT continues to recur shortly after electrical, pharmacologic, or spontaneous conversion to sinus rhythm (Fig. 263-1). Typically, VT is monomorphic. Rarely, a slow incessant monomorphic VT will fail detection by an ICD because it falls outside of the programmed detection parameters. If the arrhythmia is hemodynamically stable acutely, patients can present with symptoms of gradual cardiac decompensation. VT may become incessant due to the proarrhythmic effect of an antiarrhythmic drug such as amiodarone or a sodium channel blocker such as flecainide. Hemodynamic support may be required acutely until the precipitating factors can be corrected. Urgent catheter ablation is often warranted.

MANAGEMENT OF PATIENTS PRESENTING WITH ICD SHOCKS

A substantial number of patients who receive an ICD can be expected to have an arrhythmia that is terminated by the ICD, either by a shock or antitachycardia pacing. Although this is an expected event, it can

be a sign of impending instability, deterioration of cardiac function, or emergence of a new arrhythmia and therefore requires evaluation. Interrogation of the ICD is crucial after a patient reports a shock or symptoms of arrhythmia to confirm that the therapy was indeed delivered for a ventricular arrhythmia and not for lead malfunction or an atrial arrhythmia. After a shock and in the absence of other symptoms to suggest arrhythmia or ischemia, patients have the option of waiting until the next working day or using remote monitoring to transmit device interrogation data to their physician. However, occurrence of multiple ICD shocks constitutes a medical emergency and warrants immediate medical attention by activating the emergency medical system. Patients should never drive to the hospital themselves after receiving a shock from their ICD.

Spontaneous arrhythmias, particularly those that are converted with a shock, are associated with a subsequent increased risk of death and hospitalization in patients with depressed ventricular function. The occurrence of an arrhythmia, therefore, warrants a reevaluation for possible decline in cardiac function, emergence of ischemia, or intercurrent illness.

If the ICD therapy is appropriate for VT or VF, consideration is given to whether therapy is warranted to reduce further episodes with either antiarrhythmic drug therapy or catheter ablation. Patients who have a rare episode of VT that is appropriately terminated and who have no other evidence of instability may not need any additional therapy, particularly if the VT is terminated by antitachycardia pacing rather than a shock. Shocks reduce quality of life and can lead to posttraumatic stress disorder. In many patients, the possibility of a shock can be reduced with appropriate ICD programming. Studies have shown that antitachycardia pacing effectively terminates >70% of VT episodes, even when VT is very rapid. Most ICDs can be programmed to attempt overdrive pace termination during capacitor charge. If the arrhythmia then terminates, the shock is aborted. Appropriate programming of antitachycardia pacing is therefore critical for reducing shocks. For patients implanted with ICDs as primary prevention, programming of VF detection zones >220 beats/min significantly reduces unnecessary and inappropriate shocks. Long detection times will also help avoid unnecessary therapies for VT episodes liable to terminate spontaneously.

Recurrent symptomatic episodes of VT or VF (Fig. 263-2) warrant specific therapy with antiarrhythmic drugs or ablation as discussed for the specific arrhythmia. The beta blockers sotalol and amiodarone are the most common pharmacologic options. Amiodarone combined with beta blockers is more effective than sotalol or beta blockers alone. It is important to recognize that although VT/VF episodes may represent a deterioration of clinical status in these patients, interventions to control the arrhythmia itself may have adverse effects on outcome. Most antiarrhythmic drugs have the potential to induce bradycardia to the point of requiring pacing from the ICD that, in itself, may have deleterious effects on ventricular function. Catheter ablation is an important option for patients with monomorphic VT.

MANAGEMENT OF THE PATIENT WITH ELECTRICAL STORM

Patients should be adequately sedated to allay anxiety and provide pain relief. Recurrent VT/VF is treated using standard Advanced Cardiac Life Support guidelines; treatment includes the use of medications such as beta blockers, amiodarone, and lidocaine with correction of any metabolic abnormalities. Recordings from electrocardiogram (ECG) monitoring or an implanted ICD are important to assess whether VT

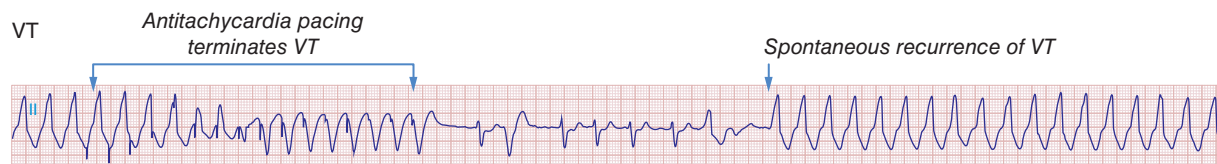


FIGURE 263-1 Example of incessant monomorphic ventricular tachycardia (VT). In the initial portion of this electrocardiogram tracing, monomorphic VT is present. A train of antitachycardia pacing (area bracketed by arrows) that is initiated at the fourth VT complex results in ventricular capture with fusion by the eighth beat and termination of VT at cessation of pacing. The patient has underlying atrial fibrillation. Multifocal premature ventricular contractions are present. VT similar in morphology to the initial VT restarts spontaneously toward the latter part of the trace (arrow).



FIGURE 263-2 Multiple implantable cardioverter-defibrillator (ICD) shocks from a subcutaneous ICD. Shown is a tracing from a patient with a subcutaneous ICD with recurrent episodes of ventricular fibrillation. The first five lines show gradually increasing amounts of ventricular ectopy and then ventricular fibrillation on the sixth line, which is terminated by a shock (*thunderbolt*) on the ninth line. The sequence repeats itself, and the patient receives a second shock that successfully terminates the arrhythmia.

Electrical storm treatments

Speed of Deployment	Stabilize rhythm	Relieve triggers	Reduce sympathetic drive
Rapid	- Defibrillation - Amiodarone - Lidocaine	- Electrolyte management - Volume removal - Coronary revascularization	- Beta blockers - Sedation and intubation - Anxiolytics
	- Quinidine - Ranolazine - Procainamide - Catheter ablation	- Overdrive pacing - Mechanical support (ECMO/IABP)	Stellate ganglion block (SGB)
Delayed		Consideration of biopsy/anti-inflammatory therapies	Cardiac surgical sympathetic denervation

FIGURE 263-3 Global strategy for managing electrical storm. Shown are considerations for stabilization of electrical storm with medication strategies and procedures. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

is monomorphic or polymorphic. The initiation and termination of tachycardia in the stored ICD electrograms may also suggest possible precipitating or aggravating factors. Sedation or general anesthesia should be considered for suppression of recurrent hemodynamically unstable ventricular arrhythmia. Percutaneous stellate ganglion block and upper thoracic epidural anesthesia may reduce cardiac sympathetic outflow and have been used to restore stability in some patients. Rarely, mechanical ventricular support with extracorporeal membrane oxygenation, percutaneous left ventricular assist device, or intra-aortic balloon pump may be considered (Fig. 263-3).

In addition to this global strategy of stabilizing the heart rhythm, reducing sympathetic drive, and relieving any triggering mechanisms for the management of electrical storm, there are some specific therapies to be considered for patients with unique electrophysiologic substrate (Fig. 263-4).

VT/VF IN THE SETTING OF MYOCARDIAL ISCHEMIA

Ischemia should be considered especially if polymorphic VT or VF is identified as the primary arrhythmia. If electrical storm is occurring in the setting of an acute coronary syndrome, emergent revascularization and alleviation of anginal symptoms should be attempted. Within the infarcted myocardium, surviving Purkinje cells can exhibit triggered automaticity and lead to recurrent episodes of polymorphic VT/VF requiring frequent cardioversions before and after revascularization. Catheter ablation of premature ventricular contractions (PVCs) that are observed to repeatedly initiate the arrhythmia can be effective (Fig. 263-5).

PVC-INITIATED POLYMORPHIC VT/VF

Similar to the post-myocardial infarction electrical storm, patients without myocardial infarction or ischemia can have PVC-initiated polymorphic VT/VF storm. This idiopathic form of VF is usually caused by triggering

PVCs originating from fascicular tissue or papillary muscles. Often, the ventricular ectopy is from scarred myocardial tissue detected on cardiac magnetic resonance imaging. Catheter ablation is indicated for this condition when antiarrhythmic medication is ineffective.

ACQUIRED OR CONGENITAL LONG QT SYNDROME

If QT prolongation causing torsades des pointes (TdP) is possible, intravenous magnesium should be administered for its immediate effect on repolarization. In addition, electrolyte repletion, especially potassium, should be aggressively pursued. Increasing the heart rate can sometimes normalize the QT interval, and thus, pharmacologic or pacing support should be considered. Isoproterenol can be used to increase a patient's sinus rate, but there is the possibility of increased ectopy with high doses of isoproterenol possibly exacerbating ventricular

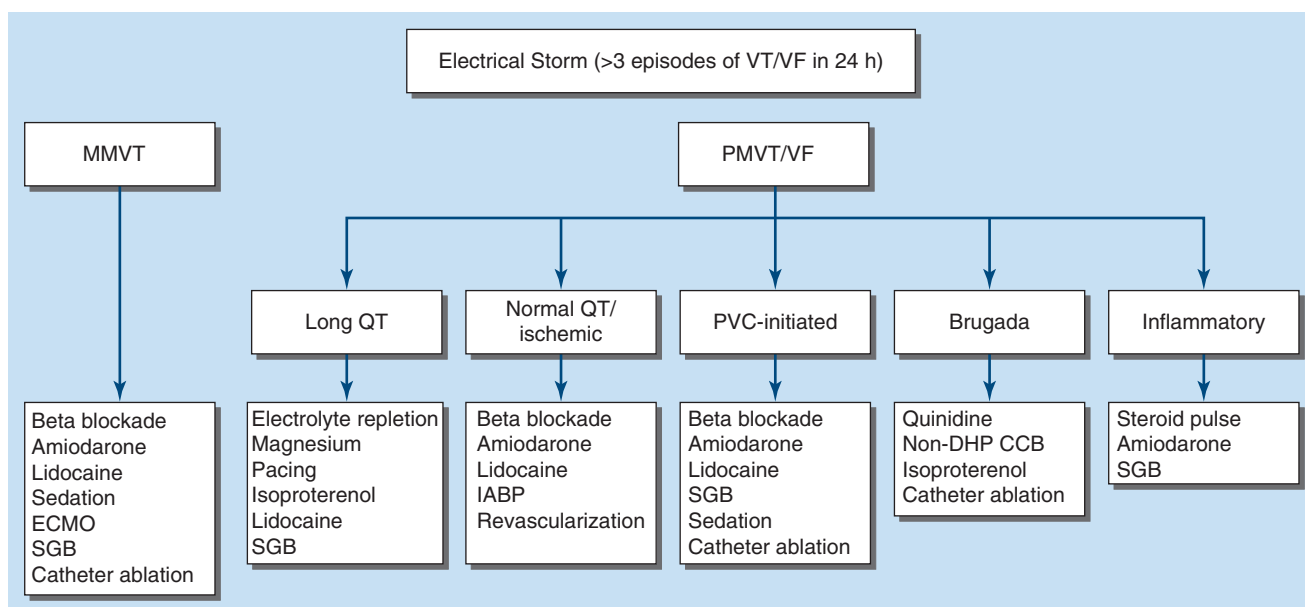


FIGURE 263-4 Management algorithm for electrical storm. Shown is a suggested strategy for managing electrical storm based on the underlying rhythm and substrate. CCB, calcium channel blocker; DHP, dihydropyridine; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MMVT, monomorphic ventricular tachycardia; PMVT, polymorphic ventricular tachycardia; PVC, premature ventricular contraction; SGB, stellate ganglion block; VF, ventricular fibrillation; VT, ventricular tachycardia.

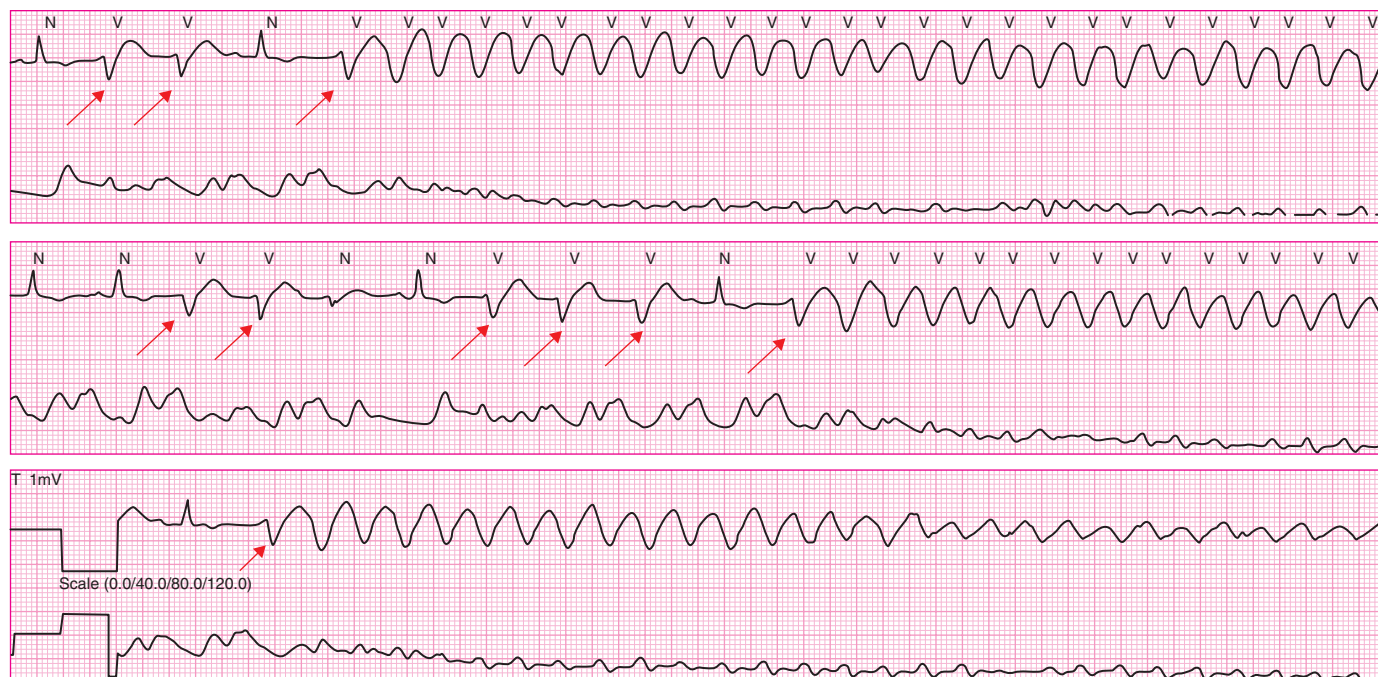


FIGURE 263-5 Premature ventricular contraction (PVC)–triggered ventricular fibrillation (VF) after myocardial infarction electrical storm. Shown is a series of monitoring strips from a patient with VF occurring in a PVC-triggered fashion after myocardial infarction. A single electrocardiogram lead and the blood pressure tracings are shown. The triggering PVCs are indicated with red arrows. The VF results in prompt hemodynamic collapse as evidenced by the blood pressure tracing.

arrhythmias. Although lidocaine can reduce the QT interval, other antiarrhythmic agents should be avoided because of their effect on repolarization.

BRUGADA SYNDROME

If the QT interval is not prolonged and a Brugada pattern of Rsr' with ST elevation in leads V_1 or V_2 is seen on resting ECG, administration of quinidine and/or isoproterenol may abolish recurrent polymorphic VT/VF episodes. Nondihydropyridine calcium channel blockers and isoproterenol have also been used to reduce arrhythmic events. An epicardial substrate-based catheter ablation over the right ventricular outflow tract has been described as a strategy for drug-refractory ventricular tachyarrhythmias in Brugada syndrome.

INFLAMMATORY CARDIOMYOPATHY

If the patient has no known previous cardiac disease, consideration should be given to an inflammatory myocarditis causing the frequent ventricular arrhythmias. Giant cell myocarditis, cardiac sarcoidosis, and certain viral myocarditis can present with VT/VF storm. An endomyocardial biopsy should be considered to potentially identify new-onset inflammatory cardiomyopathies that may require urgent anti-inflammatory therapy. Once the acute episode is controlled, strategies to prevent recurrent VT or VF should be considered.

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Section 4 Disorders of the Heart, Muscles, Valves, and Pericardium

264 Heart Failure: Pathophysiology and Diagnosis

Michael M. Givertz, Mandeep R. Mehra

CLINICAL DEFINITIONS, EPIDEMIOLOGY, AND PHENOTYPES

DEFINITIONS

Heart failure (HF) is a common final pathway for most chronic cardiovascular diseases including hypertension, coronary artery disease, and valvular heart disease. The American Heart Association/American College of Cardiology/Heart Failure Society (AHA/ACC/HFSA) guideline defines HF as a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. The European Society of Cardiology's (ESC) definition emphasizes cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise. An international consensus conference proposed a universal definition of HF that is comprehensive and practical enough to encompass formal disease stages, with universal applicability, prognostic and therapeutic validity, and acceptable sensitivity and specificity (Fig. 264-1).

Because some patients present without signs or symptoms of volume overload, the term *heart failure* is preferred over the older term

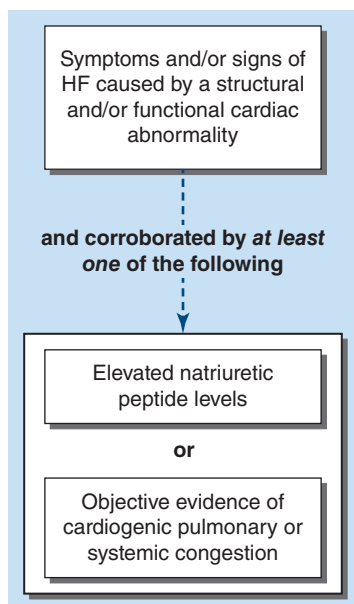


FIGURE 264-1 Universal definition of heart failure (HF). This contemporary universal definition of HF is simple but conceptually comprehensive, with near universal applicability, prognostic and therapeutic validity, and acceptable sensitivity and specificity. (Reproduced with permission from B Bozkurt et al: *Universal Definition and Classification of Heart Failure*. *J Card Fail* 27:387, 2021.)

congestive heart failure. Cardiomyopathy and left ventricular dysfunction are more general terms that describe disorders of myocardial structure and/or function, which may lead to HF. In pathophysiologic terms, HF has been defined as a syndrome characterized by elevated cardiac filling pressure and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction.

Chronic heart failure describes patients with longstanding (e.g., months to years) symptoms and/or signs of HF typically treated with medical and device therapy as described in [Chap. 265](#). Such patients are at risk of *worsening heart failure*, and when the episode resolves, the use of the term *remission* rather than *stable* HF is preferred, since these patients continue to retain the risk for further decompensation and sudden death. *Acute heart failure*, previously termed acute decompensated HF, refers to the rapid onset or worsening of symptoms of HF. Most episodes of acute HF result from worsening of chronic HF, but ~20% are due to new-onset HF that can occur in the setting of acute coronary syndrome, acute valvular dysfunction, hypertensive urgency, or postcardiotomy syndrome. Similarly, *acute pulmonary edema* in HF describes a clinical scenario in which a patient presents with rapidly worsening signs and symptoms of pulmonary congestion, typically due to severe elevation of left heart filling pressures.

■ EPIDEMIOLOGY

Global Incidence and Prevalence HF is a major cause of morbidity and mortality worldwide. An estimated 6.7 million American adults are being treated for HF, with >600,000 new cases diagnosed each year. Globally, it is estimated that 56.2 million people are living with HF with prevalence varying greatly by country. The prevalence of HF increases significantly with age, occurring in 1–2% of the population aged 40–49 years and 10% or more in adults >80 years old ([Fig. 264-2](#)). The lifetime risk of HF has increased to 24%; approximately one in four persons will develop HF in their lifetime. Projections based on National Health and Nutrition Examination Survey and U.S. Census Bureau data show that the prevalence of HF is expected to rise to 8.5 million Americans by 2030. According to the Nationwide Readmission Database, rates of HF hospitalizations in the United States declined from 2010 to 2014, followed by an increase from 2014 to 2017. HF readmissions after index hospitalization followed a similar trend. While prevalence of HF continues to rise, incidence may be decreasing due to improved recognition and treatment of cardiovascular disease

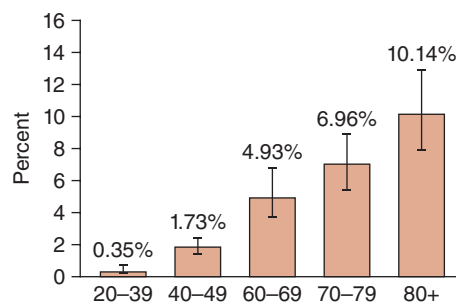


FIGURE 264-2 Heart failure prevalence by age categories. Prevalence of heart failure among U.S. adults ≥20 years of age by age, from the National Health and Nutrition Examination Survey (NHANES), 2017–2020. (Reproduced with permission from B Bozkurt et al: *J Card Fail* 29:1412, 2023.)

and its comorbidities as well as disease prevention. However, as rates of obesity rise globally, these favorable trends in HF incidence may reverse.

There are distinct racial and ethnic differences in HF epidemiology ([Fig. 264-3](#)). In community-based studies, black individuals have the highest risk of developing HF, followed by Hispanic, white, and Chinese Americans. These differences are attributed to disparities in cardiometabolic risk factors (e.g., obesity, hypertension, diabetes) as well as social determinants of health including socioeconomic status and access to health care. Similarly, studies have shown that age-adjusted rates of HF hospitalization are highest for black men, followed by black women, white men, and white women. Accurate data on HF prevalence from emerging nations are lacking. As developing nations undergo socioeconomic development, the epidemiology of HF is becoming like that of Western Europe and North America, with coronary artery disease emerging as the most common cause of HF, although hypertension remains the highest population attributable risk for HF occurrence.

Morbidity and Mortality In primary care, the overall 5-year survival following the diagnosis of HF is ~50%. For patients with severe HF, the 1-year mortality may be as high as 40%. In the United States, one in eight deaths list HF on the death certificate. The majority of these patients die of cardiovascular causes, most commonly progressive HF or sudden cardiac death. A number of clinical and laboratory parameters are independent predictors of mortality ([Table 264-1](#)). In a population-based study, hospitalizations were common after an HF diagnosis, with 83% hospitalized at least once, and 67%, 54%, and 43% hospitalized at least two, three, and four times, respectively. Following an HF admission, mortality rates range from 8–14% at 30 days to 26–37% at 1 year to up to 75% at 5 years. Readmission with HF is also common, ranging from 20–25% at 60 days to nearly

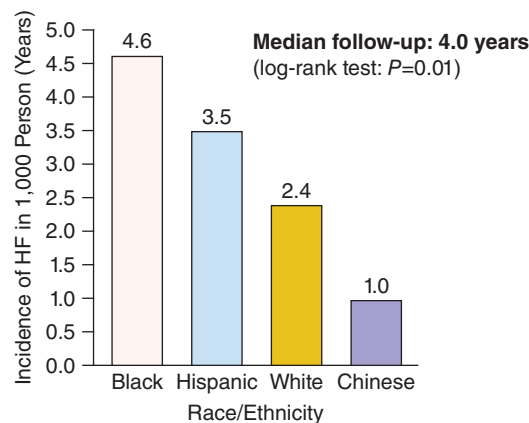


FIGURE 264-3 Incidence of heart failure (HF). HF incidence rates by race/ethnicity in the United States. (Reproduced with permission from IL Pina et al: *J Am Coll Cardiol* 78:2589, 2021.)

TABLE 264-1 Independent Predictors of Adverse Outcomes in Heart Failure

Clinical	Male sex Older age Diabetes mellitus Chronic kidney disease Coronary artery disease Advanced NYHA class ^a Presence of third heart sound or elevated JVP Decreased exercise capacity Cardiac cachexia Depression
Structural	Reduced left ventricular ejection fraction Reduced right ventricular ejection fraction Increased ventricular volumes and mass Secondary mitral or tricuspid regurgitation
Hemodynamic	Elevated pulmonary capillary wedge pressure Reduced cardiac index Reduced peak oxygen consumption Pulmonary hypertension Diastolic dysfunction
Biochemical	Worsening renal function Hyponatremia Hyperuricemia Elevated cardiac biomarkers (troponin and natriuretic peptides) Elevated plasma neurohormones (norepinephrine, renin, aldosterone, and endothelin-1)
Electrophysiologic	Tachycardia Widened QRS interval or LBBB Atrial fibrillation Ventricular ectopic activity Ventricular tachycardia and sudden death

^aSee Table 264-4.

Abbreviations: JVP, jugular venous pressure; LBBB, left bundle branch block; NYHA, New York Heart Association.

50% at 6 months. With each subsequent admission, the risk of death rises. There are racial disparities in outcomes, with black patients having higher case-fatality rates compared to white patients. Men have higher age-adjusted mortality rates for death related to HF than women; and in the United States, mortality rate from HF varies by region (highest in Midwest) and population density (highest in rural areas). Despite these statistics, the overall prognosis for patients with HF is improving due to treatment of risk factors and increased use of guideline-directed therapies.

Costs The overall cost of HF care is high (estimated \$22.3 billion in the United States in 2018) and rising. Projections for 2030 are that hospitalization costs for HF in the United States will increase to \$70 billion. Indirect costs due to lost work and productivity may equal or exceed this amount. The global economic burden of HF in 2012 was estimated at \$108 billion, with direct costs accounting for 60%. For pediatric patients with acute HF, inpatient costs are estimated at \$1 billion annually and rising.

■ PHENOTYPES AND CAUSES

HF with Reduced Versus Preserved Ejection Fraction Epidemiologic studies have shown that approximately one-half of patients who develop HF have reduced left ventricular ejection fraction (EF; $\leq 40\%$), while the other half have near normal or preserved EF ($\geq 50\%$) or are classified as having HF with mildly reduced EF (41–49%). Because most patients with HF (regardless of EF) have abnormalities in both systolic and diastolic function, the older terms of *systolic heart*

TABLE 264-2 Selected Causes of Heart Failure

Heart Failure with Reduced Ejection Fraction	
Coronary artery disease Myocardial infarction Myocardial ischemia	Nonischemic cardiomyopathy Infiltrative disorders Familial disorders Tachycardia induced
Valvular heart disease Aortic stenosis or regurgitation Mitral or tricuspid regurgitation	Toxic cardiomyopathy Chemotherapy, immunotherapy Drugs such as hydroxychloroquine Alcohol, cocaine
Congenital heart disease Intracardiac shunts Repaired defects Systemic right ventricular failure	Chronic lung/pulmonary vascular disease Cor pulmonale Pulmonary arterial hypertension
Infectious Chagas HIV	Autoimmune disease Giant cell myocarditis Lupus myocarditis
Heart Failure with Preserved Ejection Fraction	
Hypertension	Coronary artery disease
Valvular heart disease Aortic stenosis Mitral stenosis	Restrictive cardiomyopathy Amyloidosis Sarcoidosis Hemochromatosis Glycogen storage disease
Hypertrophic cardiomyopathy	Radiation therapy
Constrictive pericarditis	Aging
Myocarditis	Endomyocardial fibroelastosis
Obesity	End-stage renal disease
High-Output Heart Failure	
Thyrotoxicosis	Arteriovenous shunt
Obesity	Cirrhosis
Anemia	Vitamin B deficiency (beriberi)
Chronic lung disease	Myeloproliferative disorder

Abbreviation: HIV, human immunodeficiency virus.

failure and *diastolic heart failure* have been abandoned. Classifying patients based on their EF (HF with reduced EF [HFrEF], HF with mildly reduced EF [HFmrEF], or HF with preserved EF [HFpEF]) is important due to differences in demographics, comorbidities, and response to therapies (Chap. 265). Underlying causes of HF may be associated with reduced or preserved EF and include disorders of the coronary arteries, myocardium, pericardium, heart valves, and great vessels (Table 264-2). The diagnosis of HFpEF is often more challenging due to the need to rule out noncardiac causes of shortness of breath and/or fluid retention.

HF with Recovered EF A subgroup of patients who are diagnosed with HFrEF and treated with guideline-directed therapy have rapid or gradual improvement in EF to the normal range and are referred to as having HF with recovered EF (HFrecEF). Predictors of HFrecEF include younger age, shorter duration of HF, nonischemic etiology, smaller ventricular volumes, and absence of myocardial fibrosis. Specific clinical examples include fulminant myocarditis, stress cardiomyopathy, peripartum cardiomyopathy, and tachycardia-induced cardiomyopathy, as well as reversible toxin exposures such as chemotherapy, immunotherapy, or alcohol. Despite recovery of EF, patients may remain symptomatic due to persistent abnormalities in diastolic function, exercise-induced pulmonary hypertension, or related comorbidities (e.g., obesity). For patients who become asymptomatic, withdrawal of disease-modifying therapy can lead to recurrence of HF symptoms and decrease in EF in up to half of such patients within 6 months. In general, prognosis of patients with HFrecEF is superior to that of patients with either HFrEF or HFpEF.

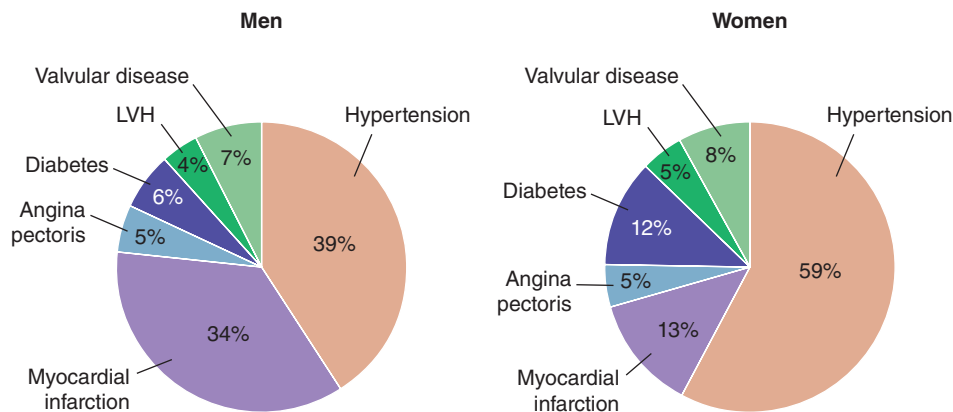


FIGURE 264-4 Population attributable risk of heart failure (HF) incidence. Based on longitudinal data from the Framingham Heart Study, the risk factors contributing most significantly to the population attributable risk (PAR) of HF in men were previous myocardial infarction and hypertension (in men, both represented equal contributions to HF PAR). In contrast, hypertension was the risk factor accounting for the majority of total PAR in women. In women, previous myocardial infarction accounted for only 13% of the PAR of HF compared with 34% in men. PAR values are developed based on individual calculations for each variable using hazard ratio and prevalence statistics. Thus, they may not, in aggregate, equal 100%. LVH, left ventricular hypertrophy. (Reproduced with permission from Givertz MM and Colucci WS. *Heart failure*. In: Libby P, editor. *Essential Atlas of Cardiovascular Disease*. Philadelphia: Current Medicine; 2009.)

HF with Mildly Reduced EF (HFmrEF) Patients with HF and an EF between 40 and 50% represent an intermediate group that are often treated for risk factors and comorbidities and with guideline-directed medical therapy similar to patients with HFrEF. They are felt to have primarily mild systolic dysfunction, but with features of diastolic dysfunction. They may also include either patients with reduced EF who experience partial improvement in their EF or those with initially preserved EF who suffer a decline in their systolic performance. The AHA/ACC/HFSA guideline requires evidence of spontaneous or provokable increased left ventricular filling pressures in their classification of HFmrEF.

Acquired Versus Familial, Congenital, and Other Disorders In developed countries, coronary artery disease is responsible for approximately two-thirds of the cases of HF, with hypertension as a principal contributor in up to 75% and diabetes mellitus in 10–40% (Fig. 264-4). Notably, population attributable risk for hypertension, obesity, diabetes mellitus, and coronary artery disease varies according to sex, race, and ethnicity (Fig. 264-5). While most cardiovascular disease underlying HF is acquired in mid and later life (Chaps. 272, 284, and 288), a wide range of congenital and inherited disorders leading to HF may be diagnosed in children and younger adults. It is currently estimated that 13.3 million people globally and approximately 467,000 U.S. adults are living with congenital heart disease (CHD). In general, adults with CHD who develop HF can be divided into one of three pathophysiologic groups: uncorrected defects with late presentation due to missed diagnosis, nonintervention, or lack of access to care; repaired or palliated defects with late valvular and/or ventricular failure; or failing single-ventricle physiology. In addition, each adult with CHD often presents with unique anatomic and physiologic challenges that affect HF and its treatment.

Inherited cardiomyopathies are also increasingly recognized in adults presenting with HF. These include more common disorders, such as hypertrophic and arrhythmogenic cardiomyopathies, and lesser known heart muscle disease related to pathogenic variants in genes encoding lamin and titin, muscular dystrophies, and mitochondrial disease. Most forms of familial cardiomyopathy are inherited in an autosomal dominant fashion. Society guidelines have been published documenting the importance of taking a detailed three-generational family history and indications for (and limitations of) clinical genetic testing.

A myriad of systemic diseases with cardiac and extracardiac manifestations (e.g., amyloidosis, sarcoidosis), autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis), infectious diseases (e.g., Chagas, HIV), and drug toxicities (chemotherapy, other prescribed or illicit agents) can result in HF with either reduced or preserved EF. In Africa and Asia, rheumatic heart disease remains a major cause of HF, especially in the young. Finally, disorders associated

with a high cardiac output state (e.g., anemia, thyrotoxicosis) are seldom associated with HF in the absence of underlying structural heart disease. However, diagnosis and treatment of high-output HF will be missed if not considered in the differential diagnosis of patients with predisposing conditions (e.g., severe obesity, severe anemia, cirrhosis, end-stage renal disease with arteriovenous fistula, Paget's disease, or nutritional deficiency such as beriberi).

PATHOPHYSIOLOGY

■ PROGRESSIVE DISEASE

HFrEF is a progressive disease that typically involves an index event followed by months to years of structural and functional cardiovascular remodeling (Fig. 264-6). The primary event may be sudden in onset, such as an acute myocardial infarction; more gradual, as occurs in the setting of chronic pressure or volume overload (with valvular heart disease); inherited, as seen with genetic cardiomyopathies; or congenital disease in origin. Despite an initial reduction in cardiac performance, patients may be asymptomatic or mildly symptomatic for prolonged periods due to the activation of compensatory mechanisms (described below) that ultimately contribute to disease progression.

Ventricular Remodeling As demonstrated in both animal and human studies, different patterns of ventricular remodeling occur in response to excess cardiac workload. Concentric hypertrophy, in which increased mass is out of proportion to chamber volume, effectively reduces wall stress under conditions of pressure overload (e.g., hypertension, aortic stenosis). By contrast, an increase in cavity size or volume (eccentric hypertrophy) occurs in volume overload conditions (e.g., aortic regurgitation, mitral regurgitation). In both forms of remodeling, an increase in ventricular mass is accompanied by changes at the *cellular level* with myocyte hypertrophy and interstitial fibrosis, at the *protein level* with alterations in calcium-handling and cytoskeletal protein abundance and/or function, and at the *molecular level* by reexpression of fetal genes (Table 264-3). In addition to cell loss from necrosis, myocytes that are unable to adapt to remodeling stimuli may be triggered to undergo apoptosis or programmed cell death. Further impairment in pump function and increased wall stress in the face of systemic vasoconstriction and loss of neurohormonal adaptation (discussed below) can lead to afterload mismatch. These events feed back on remodeling stimuli, setting up a cycle of deleterious processes resulting in clinical HF.

While our understanding of ventricular remodeling in HFrEF is well supported by animal and human studies, the mechanisms underlying HFpEF are less clear. The original descriptions of HFpEF focused on diastolic dysfunction as the primary mediator of HF

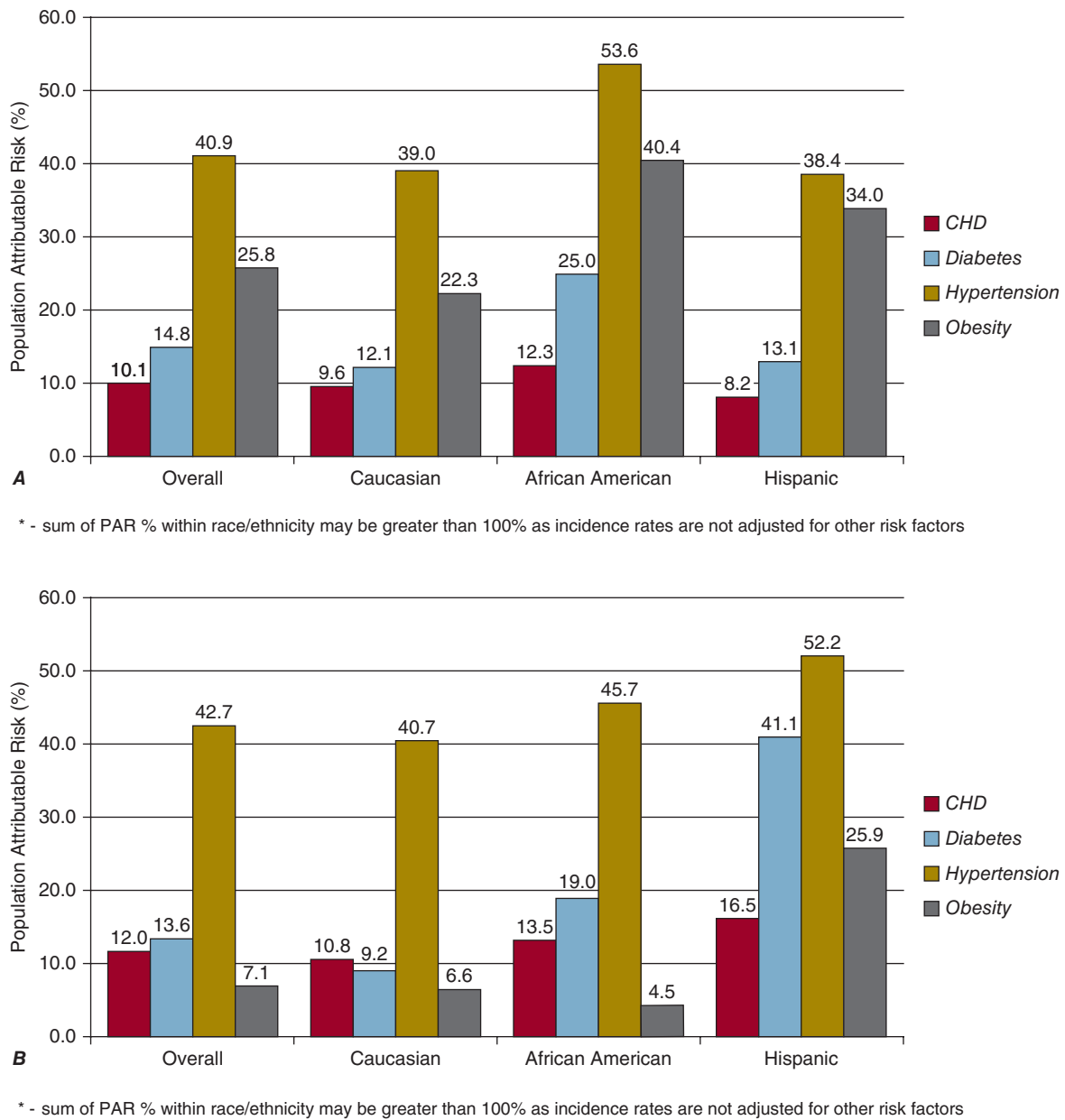


FIGURE 264-5 Population attributable risk (PAR) for heart failure (HF) by race and ethnicity. PAR* by race and ethnicity for (A) HF with preserved ejection fraction (HFpEF) and (B) HF with reduced ejection fraction (HFrEF). *Sum of PAR% within race/ethnicity may be >100% as incidence rates are not adjusted for other risk factors. CHD, coronary heart disease. (Reproduced with permission from CB Eaton, M Pettinger, J Rossouw, LW Martin et al: Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. *Circ Heart Fail* 9(10): e002883, 2016.)

signs and symptoms as exemplified in older women with hypertension. At the myocyte level, impaired uptake of cytosolic calcium into the sarcoplasmic reticulum by reductions in adenosine triphosphate explained abnormalities in myocardial relaxation. As different phenotypes of HFpEF have emerged, many pathophysiologic processes that work in concert with each other, beyond diastolic dysfunction, have been implicated in disease progression, including vascular stiffness, renal dysfunction, sodium avidity, and inflammation related to regional adiposity. Furthermore, biologic alterations including oxidative stress, impaired nitric oxide signaling leading to nitrosative stress, and insulin resistance may play a role in disease activity and inform future therapies. Autophagy is a natural process that removes unwanted cellular components by forming autophagosomes that fuse with lysosomes. While autophagy is deemed cytoprotective and adaptive, unchecked induction of autophagy may be maladaptive and a target by which disease-modifying therapy may exert beneficial effects.

MECHANISMS OF DISEASE PROGRESSION

Several compensatory mechanisms become activated during the development of HF and contribute to disease progression. Our understanding of these mechanisms derives from preclinical studies, in vivo human studies, and randomized clinical trials demonstrating benefit of therapies targeted to attenuating or reversing these biologic processes.

Neurohormonal Activation Activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) plays a critical role in the development and progression of HF. Initially, neurohormonal activation leads to increases in heart rate, blood pressure, and cardiac contractility and retention of sodium and water to augment preload and maintain cardiac output at rest and during exercise. Over time, these unchecked compensatory responses lead to excessive vasoconstriction and volume retention, electrolyte and renal abnormalities, baroreceptor dysfunction, direct myocardial toxicity, and cardiac arrhythmias. At the tissue level, neurohormonal activation

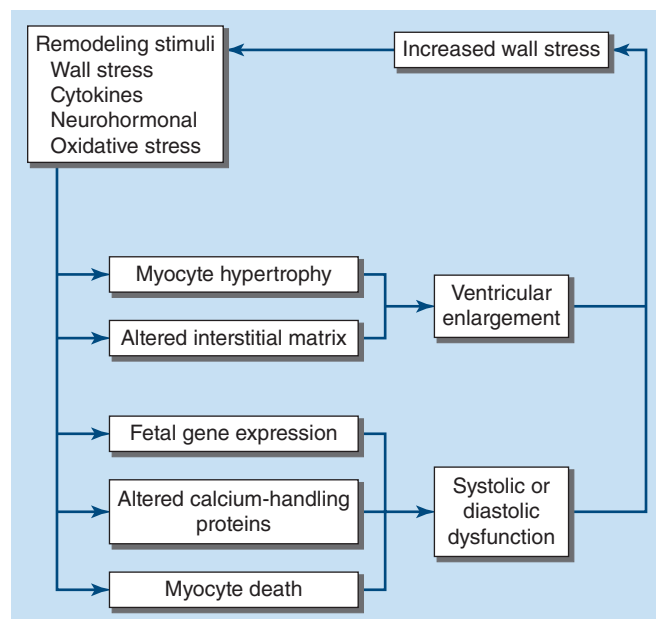


FIGURE 264-6 Remodeling stimuli in heart failure. Chronic hemodynamic stimuli such as pressure and volume overload lead to ventricular remodeling through increases in myocardial wall stress, inflammatory cytokines, signaling peptides, neuroendocrine signals, and oxidative stress. The myocardium responds with adaptive as well as maladaptive changes. Reexpression of fetal contractile proteins and calcium handling proteins may contribute to impaired contraction and relaxation. Myocytes unable to adapt might be triggered to undergo programmed cell death (apoptosis). The net result of these changes is further impairment in pump function and increased wall stress, thus completing a vicious cycle that leads to further progression of myocardial dysfunction. (Reproduced with permission from Givertz MM and Colucci WS. Heart failure. In: Libby P, editor. *Essential Atlas of Cardiovascular Disease*. Philadelphia: Current Medicine; 2009.)

contributes to remodeling of the heart, blood vessels (atherosclerosis), kidneys, and other organs (Fig. 264-7) and the development of symptomatic HF. Landmark clinical trials in HF have demonstrated that antagonism of the RAAS and SNS with renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, and beta blockers attenuates or reverses ventricular and vascular remodeling and reduces morbidity and mortality (Chap. 265).

Vasodilatory Hormones While RAAS and SNS activation contributes to disease progression in HF, a number of counterregulatory hormones are upregulated and exert beneficial effects on the heart, kidney, and vasculature. These include the natriuretic peptides (atrial

natriuretic peptide [ANP] and B-type natriuretic peptide [BNP]), prostaglandins (prostaglandin E₁ [PGE₁] and prostacyclin [PGI₂]), bradykinin, adrenomedullin, and nitric oxide. ANP and BNP are stored and released primarily from the atria and ventricles, respectively, in response to increased stretch or pressure. Beneficial actions are mediated through stimulation of guanylate cyclase and include systemic and pulmonary vasodilation, increased sodium and water excretion, inhibition of renin and aldosterone, and baroreceptor modulation. Bradykinin and natriuretic peptides are inactivated by neprilysin, a membrane-bound peptidase, which explains in part the beneficial clinical impact of angiotensin receptor-neprilysin inhibition in HF (Chap. 265). As described below, natriuretic peptide levels can be used to assist in the diagnosis and risk stratification of patients with HF.

Endothelin, Inflammatory Cytokines, and Oxidative Stress

Endothelin is a potent vasoconstrictor peptide with growth-promoting effects that may play an important role in pulmonary hypertension and right ventricular failure. Endothelin is released from a variety of vascular and inflammatory cells within the pulmonary circulation and myocardium in response to increased pressure and has direct deleterious effects on the heart, leading to myocyte hypertrophy and interstitial fibrosis. Unlike RAAS and SNS inhibition, however, endothelin blockade has not been shown to slow the progression of clinical HF due to left ventricular failure but is beneficial for treatment of pulmonary arterial hypertension and consequent right HF (Chap. 294). Other factors that have the potential to cause or contribute to ventricular remodeling in HF include inflammatory cytokines such as tumor necrosis factor (TNF) α and interleukin (IL) 1 β and reactive oxygen species such as superoxide and peroxynitrite. Potential sources of these biologically active substances are the liver and gastrointestinal tract, as described below. The role of anti-inflammatory and antioxidant therapies remains unproven.

Novel Biologic Targets Sodium-glucose cotransporter 2 (SGLT-2) is a protein located on the proximal tubule of the kidney that is responsible for reabsorption of up to 90% of filtered glucose. In patients with HF, activity of SGLT-2 contributes to sodium and water retention, endothelial dysfunction, abnormal myocardial metabolism, and impaired calcium handling. Inhibitors of SGLT-2 were developed for the treatment of type 2 diabetes mellitus to take advantage of their glycosuric and metabolic effects (Chap. 416). Subsequent large clinical trials in cardiovascular disease including HF (with or without diabetes mellitus) have demonstrated not only safety of these agents (as required by the U.S. Food and Drug Administration) but also, more importantly, beneficial effects on morbidity and mortality. Whether benefits of SGLT-2 inhibitors in HF are due primarily to diuretic effects or to effects on cardiac and vascular remodeling, proarrhythmia, renal function, and/or metabolic function, inflammation or dysregulated autophagy remains to be conclusively determined. Another pathway that is downregulated in HF and contributes to endothelial dysfunction involves cyclic guanosine monophosphate (cGMP). Oral soluble guanylate cyclase stimulators enhance the cGMP pathway and exert beneficial myocardial and vascular effects in experimental and clinical HF.

Dyssynchrony and Electrical Instability In up to one-third of patients with HF, disease progression is associated with prolongation of the QRS interval. Electrical dyssynchrony in the form of left bundle branch block (LBBB) or intraventricular conduction delay results in abnormal ventricular contraction. As discussed in Chap. 265, correction of electrical dyssynchrony with left or biventricular pacing can improve contractile function, decrease mitral regurgitation, and reverse ventricular remodeling. In patients with symptomatic HFrEF and LBBB on guideline-directed medical therapy, cardiac resynchronization therapy or LBBB (or His bundle) pacing is suggested to reduce morbidity and mortality. Other forms of electrical instability, including atrial fibrillation with inadequate rate control and frequent premature ventricular complexes, can also contribute to worsening HF. In addition to the direct impact of tachycardia and irregular rhythm on disease progression, the link between these arrhythmias and cardiac

TABLE 264-3 Mechanisms of Ventricular Remodeling

Changes in Myocyte Biology

Abnormal excitation-contraction coupling and crossbridge interaction
Fetal gene expression (e.g., β -myosin heavy chain)
 β -Adrenergic receptor desensitization
Myocyte hypertrophy
Impaired cytoskeletal proteins

Changes in Myocardial Composition

Myocyte necrosis, apoptosis, and autophagy
Interstitial and perivascular fibrosis
Matrix degradation

Changes in Ventricular Geometry

Ventricular dilation and wall thinning
Increased sphericity and displacement of papillary muscles
Atrioventricular valve regurgitation

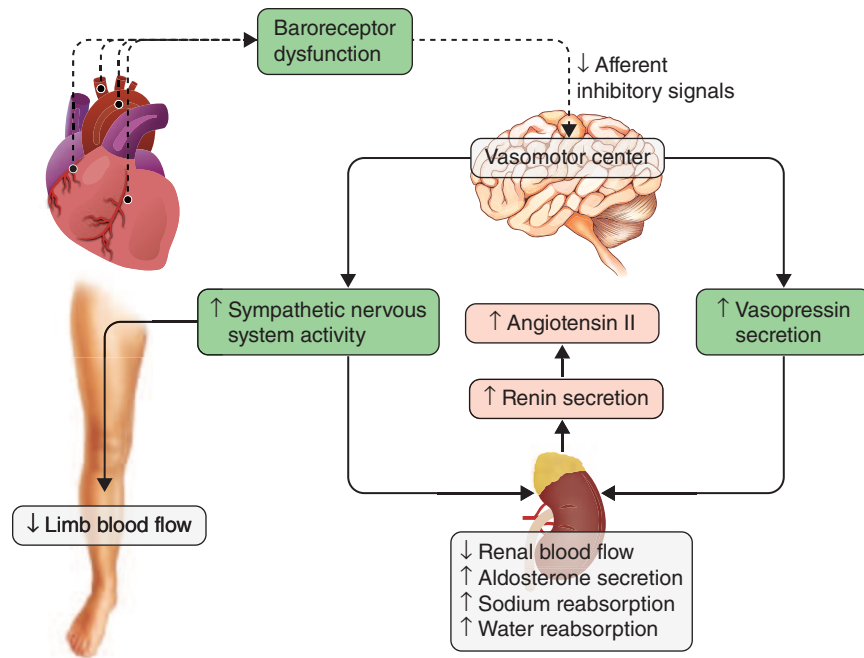


FIGURE 264-7 Activation of neurohormonal systems in heart failure. Decreased cardiac output in heart failure (HF) results in an “unloading” of high-pressure baroreceptors (circles) in the left ventricle, carotid sinus, and aortic arch, which in turn causes reduced parasympathetic tone. This decrease in afferent inhibition results in a generalized increase in efferent sympathetic tone and nonosmotic release of arginine vasopressin from the pituitary. Vasopressin is a powerful vasoconstrictor that also leads to reabsorption of free water by the kidney. Afferent signals to the central nervous system also activate sympathetic innervation of the heart, kidney, peripheral vasculature, and skeletal muscles. Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention, peripheral vasoconstriction, myocyte hypertrophy, cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short-term adaptation by maintaining blood pressure and organ perfusion, they also result in end-organ changes in the heart and circulation. (Modified from A Nohria et al: *Atlas of Heart Failure: Cardiac Function and Dysfunction*, 4th ed, WS Colucci [ed]. Philadelphia, Current Medicine Group, 2002, p. 104, and J Hartupee, DL Mann: *Nat Rev Cardiol* 14:30, 2017.)

remodeling (atrial and ventricular) involves increased wall stress, neurohormonal activation, and inflammation.

Secondary Mitral Regurgitation A large number of patients with HFrEF demonstrate evidence of mitral regurgitation. This occurs due to a distortion in the mitral valve apparatus and includes the effects of various pathophysiologic mechanisms including reduced contractile force, which leads to decreased coaptation of the leaflets, a spherical shape of the ventricle that influences length and function of the chordal-papillary muscle structure, increased dimension of the mitral annulus (and inability of the annulus to contract during systole) with reduced leaflet alignment, and dilation of the posterior wall of the left atrium, which distorts the posterior leaflet of the valve. This worsening in regurgitant volume contributes to progression in HF and adversely influences prognosis. Ensuring that this vicious cycle is interrupted is now a therapeutic target in HF. Some success has been noted by treating the mitral valve using transcatheter techniques when patients are carefully selected after exposure to optimal medical therapy when residual and significant secondary mitral regurgitation persists. Similarly, progressive tricuspid regurgitation can result from and promote adverse right ventricular remodeling. Current interventional studies are underway to assess the impact of transcatheter tricuspid valve repair or replacement in patients with advanced HF.

■ CARDIORENAL AND ABDOMINAL INTERACTIONS

An important concept underlying the pathophysiology of HF recognizes the systemic nature of disease. Thus, while the primary hemodynamic problem in HF is related to abnormalities in myocardial function (preload, afterload, and contractility), many of the presenting signs and symptoms are related to end-organ failure, including dysfunction of the kidneys, liver, and lungs. The heart and kidney interaction increases circulating volume, worsens symptoms of HF, and results in disease progression, referred to as the cardiorenal syndrome. Traditionally, this relationship was deemed to be a consequence of an

impairment in forward flow (cardiac output) leading to a decrease in renal arterial perfusion, worsening renal function, and neurohormonal activation with release of arginine vasopressin, resulting in water and sodium retention. However, evidence has emerged that renal dysfunction may not be adequately explained simply by arterial underfilling and a decline in cardiac output. Systemic venous congestion in HF with increased backward pressure may be operative in determining the development of the cardiorenal syndrome, and relief of venous congestion is associated with significant improvement in renal function in HF. Increased intraabdominal pressure, as noted in right-sided HF, and a rise in abdominal congestion are correlated with renal dysfunction in worsening HF. The interaction is not only confined to the renal component of the abdominal compartment but also involves the liver and spleen. The splanchnic veins serve as a blood reservoir and actively function in regulation of cardiac preload during changes in volume status, regulated by transmural pressure changes or mechanisms of systemic sympathetic activation. The liver and spleen participate in determining volume regulation in HF in addition to several additional interactive pathways. Splanchnic congestion results in portal vein distension and activation of the hepatorenal reflex as well as the spleno-renal reflex, which induces renal vasoconstriction. Thus, decongestion in HF by diuretic therapy or mechanical means such as ultrafiltration reduces volume, but also facilitates a decrease in pressure within the abdominal compartment, and this combination of therapeutic effect may serve to improve or stabilize renal function in HF.

■ GUT CONGESTION, THE MICROBIOME, AND INFLAMMATION

As noted above, circulating levels of proinflammatory cytokines are elevated in a number of cardiovascular disease states, including HF, and have been associated with disease progression. While the primary source of inflammation is unknown, emerging evidence suggests that an alteration in gut microbial composition and loss of microbial diversity may play an important role. The potential role of gut congestion

and also altered gut microbial composition may propagate the chronic state of inflammation and immune system dysregulation, eventually leading to progression of HFrEF. Lipopolysaccharide (LPS) is a gram-negative bacterial cell wall product whose levels are increased in patients with HF in the setting of increased intestinal permeability during periods of congestion, which is reduced with diuretic treatment. LPS is a strong stimulator of the immune system and can lead to dysregulated systemic inflammation via macrophage activation. Resulting increases in cytokines such as TNF- α , IL-1, and IL-6 in these pathways can cause progressive loss of cardiac function and also contribute to cardiac cachexia. A mechanistic link has been shown between gut microbe-dependent generation of trimethylamine *N*-oxide derived from specific dietary nutrients such as choline and carnitine and poor outcomes in patients with both acute and chronic HF. Microbe-generated uremic toxins, such as indoxyl sulfate, may play an important role in the development of HF, particularly in interaction with renal insufficiency. Thus, bowel ischemia and/or congestion depending on HF severity may be associated with morphologic and functional alterations in the intestines and result in bacterial endotoxemia and a proinflammatory state.

■ HIGH-OUTPUT STATES

Although most patients with HF, with either reduced or preserved EF, have low or normal cardiac output (CO) accompanied by elevated systemic vascular resistance (SVR), a minority of patients with HF present with a high-output state with low SVR (Table 264-2). High-output states by themselves are seldom responsible for HF, but their development in the presence of underlying cardiovascular disease can precipitate HF. For example, chronic anemia is associated with high CO when hemoglobin reduces significantly, for example, to a level that is ≤ 8 g/dL. An increase in vasodilatory metabolites and arteriolar vasodilation in response to decreased oxygen-carrying capacity of the blood in addition to a decrease in blood viscosity contributes to low SVR. Even when severe, anemia rarely causes high-output HF in the absence of a specific cardiac abnormality such as ischemic or valvular heart disease. Patients with end-stage renal disease (Chap. 323) are at particular risk of developing high-output HF when chronic anemia is exacerbated by increased flow through an arteriovenous fistula. In a recent analysis of the National Readmission Database, the most common causes of high-output HF included pulmonary disease (19.8%), severe obesity (9.9%), sepsis (9.6%), cirrhosis (8.9%), myelodysplastic syndrome (7.9%), hyperthyroidism (5.5%), and sickle cell disease (3.3%).

EVALUATION

■ HISTORY

Symptoms of Congestion: Pulmonary Versus Systemic The most common symptoms of HF are related to volume overload with elevation in pulmonary and/or systemic venous pressures. Shortness of breath is a cardinal manifestation of left HF and may arise with increasing severity as exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and dyspnea at rest. Mechanisms of dyspnea include pulmonary venous congestion and transudation of fluid into the interstitium and/or alveoli, leading to decreased lung compliance, increased airway resistance, hypoxemia, and ventilation/perfusion mismatch. Stimulation of juxtacapillary J receptors leading to an increased ventilatory drive and reduced blood flow to respiratory muscles may cause lactic acidosis and a sensation of dyspnea. The New York Heart Association (NYHA) functional classification (Table 264-4) may be used to categorize patients based on the amount of effort required to provoke breathlessness. Notably, however, NYHA class does not correlate well with other objective measures of cardiac structure (e.g., left ventricular size, EF) or function (e.g., peak oxygen consumption).

Shortness of breath when bending forward (e.g., to put on socks or tie a shoe) has been associated with an increase in cardiac filling pressure, especially in the presence of a low CO, a symptom referred to as “bendopnea.” Orthopnea refers to dyspnea that occurs in the recumbent position and is due to redistribution of fluid from the abdomen and lower body into the chest, increased work of breathing due

TABLE 264-4 New York Heart Association Functional Classification

FUNCTIONAL CLASS	LIMITATION	CLINICAL ASSESSMENT
Class I	None	Ordinary physical activity does not cause undue fatigue, dyspnea, palpitations, or angina.
Class II	Mild	Comfortable at rest. Ordinary physical activity (e.g., carrying heavy packages) may result in fatigue, dyspnea, palpitations, or angina.
Class III	Moderate	Comfortable at rest. Less than ordinary physical activity (e.g., getting dressed) leads to symptoms.
Class IV	Severe	Symptoms of heart failure or angina are present at rest and worsen with any activity.

to decreased lung compliance, and, in patients with ascites or hepatomegaly, an elevation of the diaphragm. Orthopnea typically occurs in the awake patient within 1–2 min of lying down and may be relieved by raising the head and chest with pillows or an adjustable bed. With more severe HF, patients may end up sleeping in a recliner chair or sitting up, although for some, orthopnea may diminish as symptoms of right HF appear. Orthopnea may be accompanied by nocturnal cough related to pulmonary congestion.

Paroxysmal nocturnal dyspnea (PND) refers to episodes of shortness of breath that awaken a patient suddenly from sleep with feelings of anxiety and suffocation and require sitting upright for relief. In contrast to orthopnea, PND usually occurs after prolonged recumbency, is less predictable in occurrence, and may require 30 min or longer in the upright position for relief. Episodes are often accompanied by coughing and wheezing (so-called cardiac asthma) thought to be due to increased bronchial arterial pressure leading to airway compression and interstitial pulmonary edema causing increased airway resistance. Acute pulmonary edema, due to marked elevation of the pulmonary capillary wedge pressure, is manifested by severe shortness of breath and pink, frothy sputum (Chap. 316). Cheyne-Stokes respiration and central sleep apnea may precipitate episodes of PND in HF and are related to increased sensitivity of the respiratory center to arterial PCO₂ and a prolonged circulatory time. Unlike obstructive sleep apnea, which can be treated with positive airway pressure, oral appliance, or surgical therapy, central sleep apnea has no proven therapy beyond the directed treatment of HF (Chap. 308).

In contrast to symptoms of left HF due to pulmonary venous congestion, symptoms of right HF are typically related to systemic venous congestion. Weight gain and lower extremity edema may be the initial manifestations followed by a range of gastrointestinal symptoms due to edema of the bowel wall and hepatic congestion. Abdominal bloating, anorexia, and early satiety are common. Some patients develop right upper quadrant pain related to stretching of the hepatic capsule with consequent nausea and vomiting. When these symptoms are associated with abnormal liver function tests (see below), misdiagnosis of biliary tract disease may occur. For patients with refractory right HF, the development of massive edema involving the entire body with recurrent pleural effusions and/or ascites is termed *anasarca*.

Symptoms of Reduced Perfusion Some patients with advanced HF present with symptoms related to decreased CO, sometimes referred to as *low-output syndrome*. Fatigue and weakness, particularly of the lower extremities, are nonspecific symptoms that can occur with exertion or at rest. Pathophysiology includes reduced blood flow to exercising muscles with endothelial dysfunction and increased SVR from neurohormonal activation. Chronic alterations in skeletal muscle structure and metabolism have also been demonstrated. In older patients with HF and cerebrovascular disease, reduced systemic perfusion may result in mental dullness, depressed affect, and confusion. In addition to low CO, fatigue may be caused by volume depletion, hyponatremia, iron deficiency, and medication effect (e.g., beta blockers).

Other Symptoms Patients with HF may present with mood disturbances and poor sleep, both of which may be exacerbated by nocturnal

TABLE 264-5 Precipitating Factors in Heart Failure

Patient-Related
Excess exertion or emotional stress
Excess fluid and/or sodium intake
Nonadherence with medications
Heavy alcohol use
Provider-Related
Use of medications that cause salt and water retention (e.g., NSAIDs)
Prescribed use of medications with negative inotropic properties (e.g., CCBs)
Unrecognized congestion and inadequate use of diuretics
Heart Failure–Related
Uncontrolled hypertension
Myocardial ischemia or infarction
Atrial or ventricular arrhythmias
Pulmonary embolism
Other Disease States
Systemic infection
Worsening renal or hepatic failure
Hyperthyroidism
Untreated sleep apnea
Anemia or iron deficiency syndrome

Abbreviations: CCB, calcium channel blocker; NSAID, nonsteroidal anti-inflammatory drug.

dyspnea and obstructive and/or central sleep apnea. Nocturia due to improved CO and renal perfusion in the supine position, in addition to delayed diuretic effects, can also contribute to sleep disturbances. Oliguria due to severe reductions in renal blood flow may be a sign of advanced-stage HF.

Precipitating Factors Patients with HF may be asymptomatic or mildly symptomatic either because the cardiac impairment is mild or because compensatory mechanisms help to balance or normalize cardiac function. Symptoms of HF may develop when one or more precipitating factors increase cardiac workload and disrupt the balance in favor of decompensation. Specific factors may be identified in 50–90% of admissions and can be divided into patient-related factors, provider-related factors, HF-related disease states, and other causes (Table 264-5). Inability to recognize and correct these factors promptly may lead to persistent HF despite adequate treatment.

PHYSICAL EXAMINATION

General Appearance Most patients with mild-moderate HF will appear well nourished and comfortable at rest. Even patients with more advanced disease may be in no distress after resting for a few minutes but may demonstrate immediate dyspnea with limited exertion such as walking across the room. In contrast, patients with severe HF may need to sit upright and appear anxious, diaphoretic, and dyspneic at rest with pallor due to anemia or duskiness due to low output. Other signs of severe HF include cool extremities and peripheral cyanosis. Cardiac cachexia (Table 264-6), defined partially as unintentional edema-free weight loss of >5% over 12 months, may be observed in patients with longstanding, severe HF as bitemporal or upper body muscle wasting. Contributing factors include poor oral intake due to anorexia, decreased fat absorption due to bowel wall edema, and catabolic/metabolic imbalance from activation of inflammatory cytokines (see above) and dysregulation of the growth hormone–insulin-like growth factor 1 pathway. Rarely, scleral icterus and jaundice may result from severe right HF. Others may demonstrate frailty, which can be diagnosed in the presence of sarcopenia and is exemplified by poor hand-grip strength or severely reduced gait speed.

Vital Signs With new-onset HF, heart rate rises and blood pressure may initially be increased due to sympathetic activation. In patients

TABLE 264-6 Diagnostic Criteria for Cachexia in Adults

- Underlying disease and body weight loss $\geq 5\%$ in ≤ 12 months (or BMI < 20 kg/m²)
- Plus at least three of the following five criteria
 - Decrease in muscle strength
 - Fatigue
 - Anorexia
 - Low fat-free mass index
 - Abnormal biochemistry: inflammation, anemia, low serum albumin levels

Abbreviations: BMI, body mass index.

Source: Reproduced with permission from S von Haehling et al: Nat Rev Cardiol 14:323, 2017.

with chronic HF on guideline-directed medical therapy, resting heart rate ideally should be <70–75 beats/min, and blood pressure should be in the normal to low-normal range. An irregular rhythm may be due to atrial fibrillation or flutter or frequent premature atrial or ventricular complexes. Severe HF may be associated with hypotension and narrow pulse pressure along with a rapid, thready pulse. An alternating strong and weak pulse, known as *pulsus alternans*, is attributed to reduced left ventricular contraction in every other cardiac cycle due to incomplete recovery causing reduction in the left ventricular stroke volume with each alternate beat. Respiratory rate may be normal at rest but may increase on lying down or on minimal exertion. Advanced HF may be associated with periodic breathing or Cheyne-Stokes respirations. The patient is usually unaware of the altered breathing pattern, but family members or friends may become alarmed or attribute this incorrectly to anxiety. Oxygen saturation is typically normal on room air unless there is acute pulmonary edema, underlying CHD with shunting, severe pulmonary arterial hypertension, or concomitant acute or chronic lung disease. A low-grade fever resulting from cytokine activation may occur in severe HF and subside when compensation is restored.

Jugular Venous Pulse Examination of the jugular veins provides an estimate of the right atrial pressure. Typically, the patient is examined at a 45° angle, and jugular venous pressure (JVP) is quantified in centimeters of water by estimating the height of the venous column of blood above the sternal angle in centimeters and then adding 5. In patients with mild right HF, JVP may be normal at rest (≤ 8 cm H₂O) but increase with compression of the right upper quadrant. *Hepatojugular reflux* is elicited by applying firm continuous pressure over the liver for 15–30 s while observing the neck veins. The patient must breathe normally and not strain during the maneuver. Higher levels of venous pressure approaching the angle of the jaw are common in chronic right HF. If significant tricuspid regurgitation is present, prominent V waves and Y descents may be noted. The *abdominojugular test*, defined as an increase in right atrial pressure during 10 s of firm midabdominal compression followed by an abrupt drop on pressure release, suggests elevated left-sided filling pressure. Elevation in JVP during inspiration or Kussmaul's sign may be due to severe biventricular HF and is a marker of poor outcome; it can also be seen with constrictive pericarditis or restrictive cardiomyopathy.

Lung Examination Pulmonary rales result from transudation of fluid from the intravascular space into the alveoli and airways. In general, rales are heard at the lung bases, but in severe HF or acute pulmonary edema, they may be heard throughout the lung fields. Wheezing and rhonchi can occur with congestion of the bronchial mucosa and sometimes lead to a misdiagnosis (and inappropriate treatment) of asthma or chronic obstructive pulmonary disease (COPD). Rales may be absent in patients with longstanding HF and chronically elevated pulmonary capillary wedge pressures due to increased lymphatic drainage, which prevents spillage from the interstitium into the alveoli. In biventricular or predominant right HF, bilateral pleural effusions are recognized as dullness to percussion and decreased breath sounds at the bases. When pleural effusions are unilateral, they typically involve the right side.

Cardiac Examination As discussed above, chronic HF with ventricular remodeling is typically accompanied by cardiac enlargement. The apical impulse is displaced downward and to the left and may be diffuse in dilated cardiomyopathy or sustained in pressure overloaded states such as aortic stenosis. In biventricular or severe right HF, a right ventricular heave or parasternal lift may be palpated along the left sternal border. Uncommonly, a palpable third heart sound may be present. In patients with HFpEF, precordial palpation is often normal. On auscultation, an S_3 gallop is most commonly present in patients with volume overload and tachycardia, suggests severe hemodynamic compromise, and carries negative prognostic significance. An S_4 gallop is not specific to HF but may be present in patients with HFpEF due to hypertension. Holosystolic murmurs of mitral and tricuspid regurgitation are present in the setting of advanced HF, often in the absence of structural valvular abnormalities. In patients with secondary pulmonary hypertension, a loud pulmonary component of the second heart sound may be heard.

Abdomen and Extremities Hepatomegaly is an early sign of systemic venous congestion. The liver edge may be tender due to stretching of the capsule, but with progression of right HF, tenderness may disappear. The liver edge may be pulsatile in patients with tricuspid regurgitation. Longstanding hepatic congestion may result in cardiac cirrhosis with congestive splenomegaly and mild-moderate ascites. The presence of massive ascites should lead to a search for other causes such as constrictive pericarditis or primary liver failure. Dependent lower extremity edema is common in chronic HF and is typically symmetric and pitting. Over time, chronic edema may cause reddening and induration of the skin, become weeping, or lead to cellulitis. Anasarca is used to describe massive, generalized edema involving the legs, sacrum, and abdominal wall. In patients with acute HF or younger adults with chronic HF, lower extremity edema may be absent despite marked systemic venous hypertension. Unilateral lower extremity edema may be due to deep venous thrombosis, prior trauma, or history of vein harvest for bypass surgery. Nonpitting edema that does not respond to increasing doses of diuretics may represent lymphedema that requires alternative diagnostic workup and treatment.

■ DIAGNOSIS

The diagnosis of HF is relatively straightforward when the patient presents with typical signs and symptoms; however, the signs and symptoms of HF are neither specific nor sensitive. It is therefore important for clinicians to have a high index of suspicion for HF, particularly in patients who are at increased risk, including older patients with underlying cardiovascular disease and those with comorbidities such as hypertension, diabetes, and chronic kidney disease. In this setting, additional laboratory testing and imaging should be performed (Fig. 264-8).

Routine Laboratories Standard laboratory testing in patients with HF includes a comprehensive metabolic panel, complete blood count, coagulation studies, and urinalysis. Selected patients should have assessment for diabetes, hyperlipidemia, and thyroid function. Blood urea nitrogen and creatinine levels are often elevated in moderate-severe HF due to reduced renal blood flow and/or increased renal venous pressure. Worsening renal function (Chaps. 321 and 322) due to diuretics, RAAS inhibitors, and noncardiac medications (e.g., nonsteroidal anti-inflammatory drugs) is also common. Proteinuria may be present in the setting of longstanding hypertension or diabetes or suggest an underlying systemic disease. Chronic right HF with congestive hepatomegaly can lead to modest elevations in transaminases, alkaline phosphatase, and bilirubin that should not be confused with biliary tract disease. Marked elevation in transaminases and lactic acid suggests cardiogenic shock with severe low output. In patients with cardiac cirrhosis, hypoalbuminemia may exacerbate fluid accumulation, whereas hyperammonemia contributes to altered mental status. In general, inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein, and uric acid are nonspecific and do not aid in the diagnosis of HF. Other laboratories, including

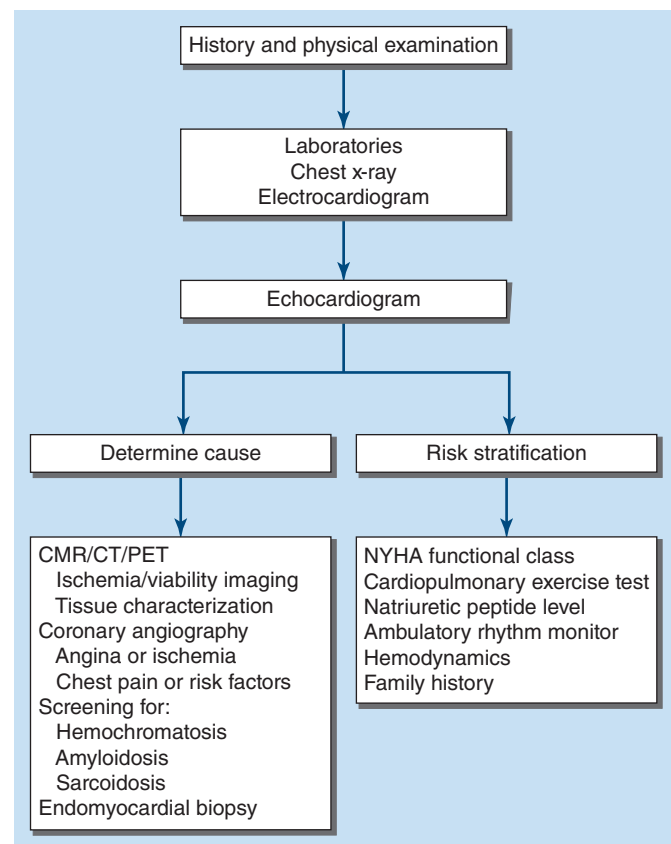


FIGURE 264-8 Initial assessment of patients presenting with heart failure. The initial evaluation starts with a thorough history and physical examination, focusing on detection of comorbidities including hypertension, diabetes, and hyperlipidemia. In addition, identification of valvular heart disease, vascular disease, history of mediastinal radiation, or exposure to cardiotoxins (e.g., chemotherapy, alcohol, or illicit drugs) may help determine underlying cause. A family history of sudden death, heart failure, arrhythmias, or cardiomyopathy is also useful. Routine laboratory evaluation (see text) should also be performed. Chest x-ray is useful to detect cardiomegaly and fluid overload and to rule out pulmonary disease. A 12-lead electrocardiogram should be performed to detect abnormalities of cardiac rhythm and conduction, left ventricular hypertrophy, and evidence of myocardial ischemia or infarction. Two-dimensional echocardiography with Doppler imaging is indicated to assess cardiovascular structure and function and detect abnormalities of the myocardium, heart valves, or pericardium. Further imaging and laboratory studies aimed at identifying a specific cause of cardiomyopathy depend on information obtained from the history and physical examination. In all patients, risk stratification should be performed to assess severity of illness, guide therapy, and provide prognosis to patient and family. CMR, cardiac magnetic resonance imaging; CT, computed tomography; NYHA, New York Heart Association; PET, positron emission tomography.

antinuclear antibodies, rheumatoid factor, serum free light chains, serum protein electrophoresis, ferritin, ceruloplasmin, hepatitis C, and HIV, are reserved for targeted testing.

Electrolyte abnormalities seen in HF include hyponatremia due to sodium restriction, diuretic therapy, and vasopressin-mediated free water retention. Hyponatremia is a negative prognostic indicator at the time of HF hospitalization and predicts decreased long-term survival (Table 264-1). Hypokalemia is most often due to thiazide or loop diuretics given without oral potassium supplementation but may also result from increased aldosterone levels. Hyperkalemia may result from marked reductions in glomerular filtration rate and is exacerbated by use of RAAS inhibitors, potassium-sparing diuretics, and potassium supplements (Chap. 265). Hypo- or hyperkalemia may lead to atrial or ventricular arrhythmias. Hypophosphatemia and hypomagnesemia are commonly associated with chronic alcohol use.

Anemia is not diagnostic of HF, but when present, it may exacerbate underlying ischemic heart disease or decrease quality of life in patients with HF due to any cause and should be corrected. Rarely, severe

anemia may cause high-output HF typically in the presence of underlying cardiovascular disease. The presence of iron deficiency (with or without anemia) is increasingly recognized in patients with chronic HF and has been attributed to decreased gut absorption, impaired hepatic storage, and chronic blood loss. Repletion with IV iron (but not oral iron) results in improved symptoms and exercise capacity and reduced HF hospitalizations, but its effect on survival remains uncertain.

Chest X-Ray Major abnormalities on chest imaging associated with left HF include enlarged cardiac silhouette (cardiothoracic ratio >0.5) and pulmonary venous congestion. Early radiologic signs of acute HF include upper zone venous redistribution and thickening of interlobular septa. When the pulmonary capillary wedge pressure is moderate to severely elevated, alveolar edema can present as diffuse haziness extending downward toward the lower lung fields. The absence of these findings in patients with chronic HF reflects the increased capacity of the lymphatics to remove interstitial and/or pulmonary fluid. Pleural effusions of varying size and distribution are common in biventricular HF. Chest x-ray can also be used to identify noncardiac causes of dyspnea (e.g., pneumonia, COPD).

Electrocardiogram No specific electrocardiographic (ECG) pattern is diagnostic of HF. Rather, the ECG may provide important information regarding presence of underlying cardiac disease. For example, left ventricular hypertrophy and left atrial enlargement suggest HFpEF due to hypertension, aortic stenosis, or hypertrophic cardiomyopathy. The presence of Q waves or infarction is suggestive of ischemic heart disease, whereas Q waves with reduced QRS voltage (pseudo-infarct pattern) may be seen with restrictive or infiltrative cardiomyopathies (e.g., amyloid). Conduction system disease should raise concern for cardiac sarcoid or Chagas cardiomyopathy in the right clinical setting.

Paroxysmal or persistent atrial fibrillation is present in up to 40% of patients with chronic HF and is an indication for anticoagulation. Premature ventricular complexes (PVCs) and nonsustained ventricular tachycardia can reflect worsening HF and are markers of increased risk. Conversely, frequent PVCs can cause cardiomyopathy that may be treated successfully with ablation (Chap. 260). Finally, determination of the QRS width and presence of LBBB is used to ascertain whether the patient may benefit from cardiac resynchronization or left bundle branch (or His bundle) pacing therapy.

Noninvasive Imaging Noninvasive cardiac imaging (Chap. 248) is essential for the diagnosis, evaluation, and management of HF. Two-dimensional echocardiography provides an accurate and rapid determination of ventricular size and function and valvular morphology and function and can detect intracavitary thrombi and pericardial effusions. When left ventricular ejection fraction (LVEF) is $\geq 50\%$, systolic function is deemed to be normal. Myocardial strain rate imaging using speckle tracking can add incremental value to LVEF and carries prognostic value. Doppler techniques can be used to estimate CO, pulmonary artery pressures, and valve areas, and may detect abnormalities in left ventricular diastolic filling in patients with HFpEF. For patients with end-stage HF, echocardiography is critical for assessment of right ventricular function before and after mechanical circulatory support and heart transplant. Transesophageal echocardiogram (TEE) or cardiac computed tomography (CT) with contrast is indicated to rule out left atrial appendage thrombus prior to cardioversion and can assess aortic or mitral valve pathology in planning for transcatheter valvular replacement or repair. TEE can also be used to assess for endocarditis in patients with bacteremia or acute valvular regurgitation.

Cardiac magnetic resonance imaging (CMR) has emerged as a highly accurate and quantitative tool for evaluation of left ventricular mass, volumes, and function and for determining specific causes of HF (e.g., ischemic cardiomyopathy, myocarditis, amyloidosis, hemochromatosis). CMR is particularly helpful in defining multiple anatomic and functional abnormalities in adults with CHD. Serial CMR studies can assess ventricular remodeling in response to therapy and are useful in clinical research. For patients who cannot undergo CMR (e.g., due

to implantable devices), cardiac CT is particularly helpful to rule out pericardial disease or left ventricular apical thrombus. Coronary CT angiography has also emerged as a useful noninvasive test to rule out obstructive coronary artery disease as a cause of HF. While limited by availability and cost, cardiac positron emission tomography (PET) plays a role in evaluating the extent of ischemia, infarction, or hibernating myocardium in patients with coronary artery disease and, in the case of sarcoidosis, can reliably determine the severity and distribution of cardiac inflammation.

Cardiopulmonary Exercise Testing While not routinely performed in HF, cardiopulmonary exercise testing using a symptom-limited, ramp protocol can provide an objective assessment of peak functional capacity in patients being evaluated for mechanical circulatory support or heart transplant (Chap. 271). Several parameters including absolute and percent-predicted peak oxygen consumption (VO_2) and ventilatory efficiency (VE; assessed by the VE/VCO_2 slope) are independent predictors of survival. Additional data including heart rate and blood pressure response to exercise and exercise-induced arrhythmias can also be assessed. This test may also be useful in defining the cause of dyspnea when the diagnosis is uncertain.

Biomarkers Circulating levels of natriuretic peptides are useful, adjunctive tools in the diagnosis of HF. BNP and N-terminal pro-BNP (NT-proBNP) are released from the atria and ventricles in response to increased wall stress. Patients with HFpEF tend to have higher levels than patients with HFpEF, whereas levels may be falsely low in obesity. In ambulatory patients with dyspnea, the measurement of BNP or NT-proBNP is useful to support clinical decision-making regarding the diagnosis of HF, especially in the setting of clinical uncertainty or with concomitant lung disease. Moreover, natriuretic peptide levels can be used to establish disease severity and prognosis in chronic HF and may help to guide optimal dosing of medical therapy in stable outpatients. Importantly, many noncardiac factors, including age, female sex, and chronic kidney disease, increase natriuretic peptide levels. Other cardiovascular diseases including atrial fibrillation, pulmonary embolism, and pulmonary arterial hypertension can also increase BNP levels. Galectin-3 and soluble ST2 (suppression of tumorigenicity 2 protein) are newer biomarkers that have been approved for assessment of prognosis in HF but are not widely used. Biomarkers of renal injury require further study in HF, although use of cystatin C to measure renal function may be more accurate than a creatinine, which can be influenced by muscle mass.

Invasive Studies In the intensive care setting, assessment of cardiac filling pressures and CO may be necessary to differentiate cardiogenic from noncardiogenic pulmonary edema and manage hemodynamic instability. Placement of a pulmonary artery catheter can be performed safely at the bedside and used to determine response to intravenous vasoactive and diuretic therapy in severe HF. Simultaneous measurement of right and left heart filling pressures in the cardiac catheterization laboratory can be used to distinguish restrictive cardiomyopathy from constrictive pericarditis. Coronary angiography is indicated to exclude ischemic heart disease as an underlying, potentially reversible cause of left ventricular dysfunction. The management of coronary artery disease in the setting of chronic HF is discussed in Chaps. 285–287. If echocardiographic windows are suboptimal, left ventriculography can provide an assessment of left ventricular size and function and severity of mitral regurgitation. The role of right ventricular endomyocardial biopsy in the management of HF and cardiomyopathy remains controversial. Indications include detection of myocarditis (lymphocytic, eosinophilic, sarcoid, or giant cell), diagnosis of cardiac amyloidosis and chemotherapy- or immunotherapy-related left ventricular failure, and screening for cardiac allograft rejection following heart transplant.

COMORBIDITIES

■ DIABETES

Type 2 diabetes mellitus is a risk factor for the development of HF (Table 264-7) and increases the risk of morbidity and mortality in

TABLE 264-7 Mechanisms That Contribute to Development of Heart Failure in Patients with Type 2 Diabetes Mellitus

Altered myocardial substrate
Abnormal mitochondrial bioenergetics
Oxidative stress and inflammation
Lipotoxicity
Endoplasmic reticulum stress
Impaired insulin signaling
β ₂ -Adrenergic receptor signaling
G protein–coupled receptor kinase 2 signaling
RAAS activation
Advanced glycation end products
Autophagy

Abbreviation: RAAS, renin-angiotensin-aldosterone system.
Source: Modified with permission from TA Zelniker: Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. J Am Coll Cardiol 75:422, 2020.

patients with established disease. In ambulatory HF cohorts, the prevalence of diabetes ranges from 10 to 40%, with prevalence even higher in patients hospitalized with HF. When the two diseases coexist, patients are at increased risk for adverse outcomes, worse quality of life, and higher costs of care. Recent data from cardiovascular outcomes trials demonstrate that HF is a critical outcome in patients with diabetes and that glucose-lowering therapies can impact morbidity and mortality. As discussed above, SGLT-2 inhibitors in particular have not only been shown to be safe in patients with HF but can also improve renal function, enhance quality of life, increase LVEF, and decrease the risk of hospitalization and death. Use of other guideline-directed medical therapy is indicated in patients with HF regardless of diabetes status.

SLEEP APNEA

Sleep-disordered breathing is common in HF, with increased incidence of both obstructive sleep apnea and central sleep apnea (Chap. 308). The pathophysiologic link between these disorders has been studied in both animal models and humans and includes increased afterload, decreased preload, intermittent hypoxia, and sympathetic activation. Increase in sympathetic tone can provoke ischemia and arrhythmias and complicate blood pressure management. Approximately one-third of patients with HF and sleep-disordered breathing have central sleep apnea, which is associated with increased mortality independent of other known risk factors. In patients with HFrEF and obstructive sleep apnea, continuous positive airway pressure has been shown to improve quality of life, decrease blood pressure and arrhythmias, and increase LVEF. Unlike obstructive sleep apnea, there is no proven therapy for central sleep apnea, although phrenic or hypoglossal nerve pacing may provide benefit in some cases.

OBESITY

Similar to diabetes, obesity is both a risk factor for the development of HF and highly prevalent in patients with HF. In particular, obesity is common in patients with HFpEF and complicates the assessment of volume status in both ambulatory and inpatient settings. Unlike diabetes, the risk of morbidity and mortality in patients with obesity and HF is complex. The obesity paradox refers to the observation that obese patients diagnosed with HF have a more favorable prognosis than patients with low or even normal body mass index. While weight loss has been shown to improve quality of life and exercise capacity and may contribute to reverse ventricular remodeling in patients with HF, the impact on survival is unknown. Large randomized clinical trials are assessing safety and efficacy of glucagon-like peptide-1 (GLP-1) agonists such as semaglutide in patients with heart failure and obesity.

DEPRESSION

Depression is an independent risk factor for adverse outcomes in HF (Table 264-1), especially in older women. The mechanisms

TABLE 264-8 Differential Diagnosis of Heart Failure

SYMPTOM OR SIGN	DIFFERENTIAL DIAGNOSIS
Dyspnea	Chronic lung disease Pulmonary arterial hypertension Neuromuscular disease Anemia Iron-deficiency anemia
Edema	Venous insufficiency Nephrotic syndrome Deep vein thrombosis Lymphedema
Ascites	Hepatic cirrhosis Portal vein thrombosis Malignant carcinomatosis
Pleural effusion(s)	Chronic infection Lung cancer Collagen vascular or rheumatologic disease
Jugular venous distension	Constrictive pericarditis Pericardial effusion Superior vena cava syndrome

underlying this risk remain unknown but may involve neuroendocrine dysfunction and systemic inflammation, as well as contributions from poor sleep, decreased appetite, and adverse effects of medications and alcohol. The AHA recommends screening for depression among patients with cardiovascular disease including HF using validated patient health questionnaires. Selective serotonin reuptake inhibitors are safe for treating depression in HF but do not appear to affect the natural history of disease. The effects of cognitive behavioral therapy and the collaborative care model, as well as newer therapies such as transcranial magnetic stimulation, on HF morbidity and mortality require further study.

DIFFERENTIAL DIAGNOSIS

Many symptoms and signs suggesting HF may be caused by other conditions (Table 264-8). In a patient with dyspnea, the clinician must distinguish cardiac from pulmonary causes, although the differentiation may be difficult. For example, orthopnea may be a well-established symptom in some patients with severe chronic lung disease. Patients with underlying pulmonary disease may also experience episodic shortness of breath during sleep that mimics PND. In chronic lung disease, this is usually due to accumulation of tracheobronchial secretions and is relieved by coughing and expectoration, whereas in cardiac disease, the patient has to sit upright. Wheezing caused by bronchoconstriction may be a prominent symptom when left ventricular failure supervenes in individuals with reactive airways disease. Patients with cardiac asthma may be more likely to exhibit diaphoresis and varying degrees of cyanosis compared to patients with bronchial asthma. Differentiating dyspnea related to HF versus pulmonary disease may be impossible when the diseases coexist, a situation that is common in chronically ill older patients with active or prior smoking. Following effective diuresis, pulmonary function tests may help to determine the predominant cause of dyspnea. In ambulatory patients with advanced HF, cardiopulmonary exercise testing can also help to make this distinction. Finally, a very low BNP or NT-proBNP level may be helpful in excluding HF as the cause of dyspnea in nonobese patients.

Apart from pulmonary disease, HF needs to be distinguished from conditions in which congestion results from abnormal salt and water retention but in which cardiac structure and function are normal (e.g., acute or chronic kidney disease) and from noncardiac causes of pulmonary edema (e.g., acute respiratory distress syndrome). Non-HF causes of lower extremity edema such as venous insufficiency, lymphedema, and obesity should also be considered.

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ejection fraction (HFrEF; LVEF $\leq 40\%$) have provided a rich evidence base that supports the efficacy of stepped pharmacologic therapy with renin-angiotensin-aldosterone system (RAAS) antagonists (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists), neprilysin inhibitors, β -adrenergic receptor antagonists, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors as a complement to device-based treatment with cardiac resynchronization therapy and implantable cardioverter-defibrillators. By contrast, treatment of patients with symptomatic chronic HF and mildly reduced (HFmrEF; LVEF 41–49%) or preserved ejection fraction (HFpEF; LVEF $\geq 50\%$) has, until recently, been symptom-focused owing to the lack of evidence-based therapies but is evolving in the wake of favorable results from recently reported trials of SGLT-2 inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and angiotensin-neprilysin inhibitors. Even with effective therapy, patients with HFrEF, HFmrEF, and HFpEF are at risk for clinical deterioration, typically because of progressive sodium and fluid retention that fuels the development of congestive symptoms and acute decompensated HF (ADHF). Management of these exacerbations (frequently hospital-based) is heavily focused on hemodynamic stabilization, decongestion, and institution of appropriate disease-modifying therapy in the transition back to chronic ambulatory management. Recurrent episodes of ADHF despite careful follow-up and effective treatment may signal the onset of an advanced or refractory HF phenotype (ACC/AHA stage D) in which the risk of mortality from sudden death or end-stage HF is high, and consideration of salvage therapies including cardiac transplant or mechanical circulatory support may be appropriate prior to escalation to palliative measures ([Chap. 271](#)).

HEART FAILURE WITH MILDLY REDUCED OR PRESERVED EJECTION FRACTION

GENERAL PRINCIPLES

Although clinical trials of RAAS antagonists, digoxin, β -adrenergic receptor blockers, and neprilysin inhibitors have been conducted in patients with HFpEF, none has conclusively demonstrated a mortality reduction. Variable benefits, measured in the form of reduced HF hospitalizations, have been seen with mineralocorticoid receptor antagonists, angiotensin receptor blockers, and angiotensin receptor-neprilysin inhibitors, but benefits are principally confined to those with LVEF below the normal range (<0.60). This has led many to recommend that patients with HFmrEF should be treated with the same therapies as those with HFrEF. Patients with higher ejection fraction (EF) remain a therapeutic challenge. In the absence of specific pharmacologic therapies proven to improve clinical outcomes, management of patients with HFpEF has historically been focused on improving symptoms and effort tolerance through lifestyle modification, control of congestion, stabilization of heart rhythm (particularly in those with atrial fibrillation), control of blood pressure to guideline-recommended targets, and management of comorbidities that may contribute to disease progression (including, for example, obesity, obstructive lung disease, obstructive sleep apnea, diabetes/insulin resistance, anemia, iron deficiency, and chronic kidney disease). More recently, however, targeted pharmacologic therapy is emerging, with clinical trials of SGLT-2 inhibitors supporting use of these agents to reduce cardiovascular mortality and HF hospitalizations in HFmrEF and HFpEF. Trials of angiotensin receptor-neprilysin inhibitors and GLP-1 agonists (in obese patients) also suggest possible benefits in selected HFpEF patients.

CLINICAL TRIALS IN HFPEF

Attempts to export the benefits of drugs that improve clinical outcomes in patients with HFrEF, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β -adrenergic receptor blockers, digoxin, and mineralocorticoid receptor antagonists, to those with HFpEF have generally been unsuccessful. The Candesartan in Heart Failure—Assessment of Mortality and Morbidity (CHARM) Preserved study showed a statistically significant reduction in HF hospitalizations but no difference in all-cause mortality in patients with HFpEF who were treated with the ARB candesartan.

265

Heart Failure: Management

Akshay Desai, Mandeep R. Mehra

Clinical management of patients with heart failure (HF) varies widely based on the clinical phenotype at presentation. Those in the earliest stage of disease with asymptomatic ventricular dysfunction (American College of Cardiology [ACC]/American Heart Association [AHA] stage B) may be amenable to treatment with neurohormonal antagonists, including angiotensin-converting inhibitors and β -adrenergic receptor antagonists, with the goal of facilitating ventricular recovery and preventing the development of clinical HF (not further discussed). Those with symptomatic HF (ACC/AHA stage C) comprise a heterogeneous group in whom the approach to therapy is differentiated largely based on measurement of the left ventricular ejection fraction (LVEF). Data from prospective, randomized clinical outcomes trials enrolling patients with symptomatic chronic HF and reduced

Similarly, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial demonstrated no differences in the composite of cardiovascular death or HF hospitalization during treatment with the ARB irbesartan compared with placebo. Apparent early benefits of the ACE inhibitor perindopril on HF hospitalizations and functional capacity in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study were attenuated over longer-duration follow-up. The Digitalis Investigation Group (DIG) Ancillary Trial found no impact of digoxin on all-cause mortality or on all-cause or cardiovascular hospitalization among patients with chronic HF, EF >45%, and sinus rhythm, although a modest reduction in HF hospitalizations was noted. While no dedicated study of beta blockers has been conducted in HFpEF, the subgroup of elderly patients with prior hospitalization and HFpEF enrolled in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial of nebivolol, a vasodilating beta blocker, did not appear to experience significant reductions in all-cause or cardiovascular mortality.

Regarding *mineralocorticoid receptor antagonists*, which have potent antifibrotic effects in HFrEF, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial explored the potential benefit of spironolactone compared to placebo in HFpEF. This trial demonstrated no improvement in the primary composite endpoint of cardiovascular death, HF hospitalizations, or aborted cardiac arrest but did show a reduction in HF hospitalizations among those allocated to spironolactone. Post hoc analyses of the study suggested significant regional differences in the baseline characteristics, event rates, adverse effects, and adherence to spironolactone among patients randomized in Russia and the Republic of Georgia compared with those randomized in the Americas that raised concerns about study conduct in Russian and Georgian sites. Apparent reductions in cardiovascular death and HF hospitalization associated with spironolactone among the subgroup of patients randomized in the Americas suggest that these study design issues may have obscured a signal of spironolactone benefit. These data have supported a weak recommendation for spironolactone in patients with HFpEF who meet the inclusion criteria for the TOPCAT trial and are at low risk for adverse effects, including hyperkalemia and worsening renal function, in the most recent U.S. and European guidelines. However, the results of the Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study in which spironolactone improved echocardiographic indices of diastolic dysfunction but failed to improve exercise capacity, symptoms, or quality-of-life (QOL) measures highlight the need for further study. Ongoing trials, including the registry-based Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction (SPIRRIT-HFpEF) (SPIRRIT-HFpEF; clinicaltrials.gov identifier NCT02901184) and the randomized Study to Evaluate the Efficacy and Safety of Finerenone on Morbidity and Mortality in Participants with Heart Failure and Left Ventricular Ejection Fraction Greater than or Equal to 40% (FINEARTS-HF; clinicaltrials.gov identifier: NCT04435626) may provide additional insight in this regard.

Addition of the SGLT-2 inhibitors dapagliflozin and empagliflozin to guideline-directed medical therapy of HFrEF has been associated with reductions in cardiovascular mortality and HF hospitalization among patients with and without diabetes mellitus enrolled in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-REDUCED) trials. These benefits have recently been extended to the population of patients with symptomatic HF and LVEF >40% based on observed reductions in the composite of cardiovascular death or HF hospitalization among those assigned to SGLT-2 inhibitors compared to placebo in the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-PRESERVED) trials. Pooled analysis of the data from these trials is associated with a reduction in the composite or cardiovascular death or HF hospitalization.

These results have driven updates to treatment guidelines in the United States and Europe, which now embrace use of SGLT-2 inhibitors as foundational therapy in patients with symptomatic HF regardless of EF. However, cost-effectiveness analyses suggest that these agents may be of low to intermediate economic value, which may limit access until price reductions ensue.

■ OTHER THERAPEUTIC TARGETS

Beyond pharmacologic therapy, small studies of exercise training and cardiac rehabilitation in patients with HFpEF have suggested benefits on functional capacity and QOL, indicating a possible role for lifestyle interventions to improve cardiorespiratory fitness in this population. For obese patients with HFpEF, aggressive efforts at weight loss (including bariatric surgery) may also be associated with improvements in hemodynamics and exercise capacity. Recently, the randomized STEP-HFpEF trial of the once-weekly GLP-1 agonist semaglutide in obese (body mass index ≥ 30 kg/m²) HFpEF patients without diabetes mellitus demonstrated improvements in functional capacity and QOL associated with incremental weight loss of nearly 12% relative to placebo. Several ongoing trials including STEP-HFpEF DM (Semaglutide Treatment Effect in People with Obesity and HFpEF and Type 2 Diabetes; clinicaltrials.gov identifier: NCT04916470) and the SUMMIT trial of the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonist tirzepatide (clinicaltrials.gov identifier: NCT04847557) will provide further data for clinical utility in this population.

A novel paradigm for understanding the pathophysiology of HFpEF has focused on the role of microvascular endothelial inflammation driven by comorbidities that results in impaired nitric oxide (NO) signaling and associated increases in myocardial stiffening. This paradigm has emphasized the potential for improving outcomes in HFpEF by enhancing NO bioavailability and improving downstream protein kinase G–based signaling. In this regard, a small trial demonstrated that the phosphodiesterase-5 inhibitor *sildenafil* improved filling pressures and right ventricular function in a cohort of HFpEF patients with pulmonary venous hypertension. This finding led to the phase 2 trial, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX), in HFpEF patients (LVEF >50%) with New York Heart Association (NYHA) functional class II or III symptoms, who received sildenafil at 20 mg three times daily for 3 months, followed by 60 mg three times daily for another 3 months, compared with a placebo. There was no improvement in functional capacity, QOL, or other clinical and surrogate parameters in those allocated to sildenafil compared to placebo. On the premise that *nitrates*, which are NO donors, might improve preload, coronary perfusion, endothelial function, and exercise tolerance, the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) study was conducted. Isosorbide mononitrate did not improve QOL or submaximal exercise capacity and decreased overall activity levels in treated patients. *Inorganic nitrate* compounds have also been shown to enhance NO signaling but did not improve functional capacity compared to placebo among patients with HFpEF randomized in the Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure with Preserved Ejection Fraction (INDIE-HFpEF) trial.

Neprilysin inhibition is known to increase circulating levels of various vasoactive peptides, including the natriuretic peptides, which may facilitate cyclic guanosine 3',5'-monophosphate–based signaling, enhance myocardial relaxation, and reduce ventricular hypertrophy. Composite *angiotensin receptor-neprilysin inhibition* (ARNI) with sacubitril-valsartan reduced cardiovascular mortality, overall mortality, and HF hospitalization compared with enalapril among patients with HFrEF randomized in the PARADIGM-HF trial. The PARAGON-HF trial randomized 4822 patients with symptomatic HFpEF (LVEF $\geq 45\%$), elevated natriuretic peptides, and structural heart disease to treatment with either sacubitril-valsartan or valsartan with the novel composite primary endpoint of cardiovascular death and total hospitalizations for HF. Although there was a 13% reduction in the rate of the primary composite endpoint in those allocated to sacubitril-valsartan, this result narrowly missed the margin for statistical significance in the

Heart Failure with Preserved Ejection Fraction: Pathology and Management

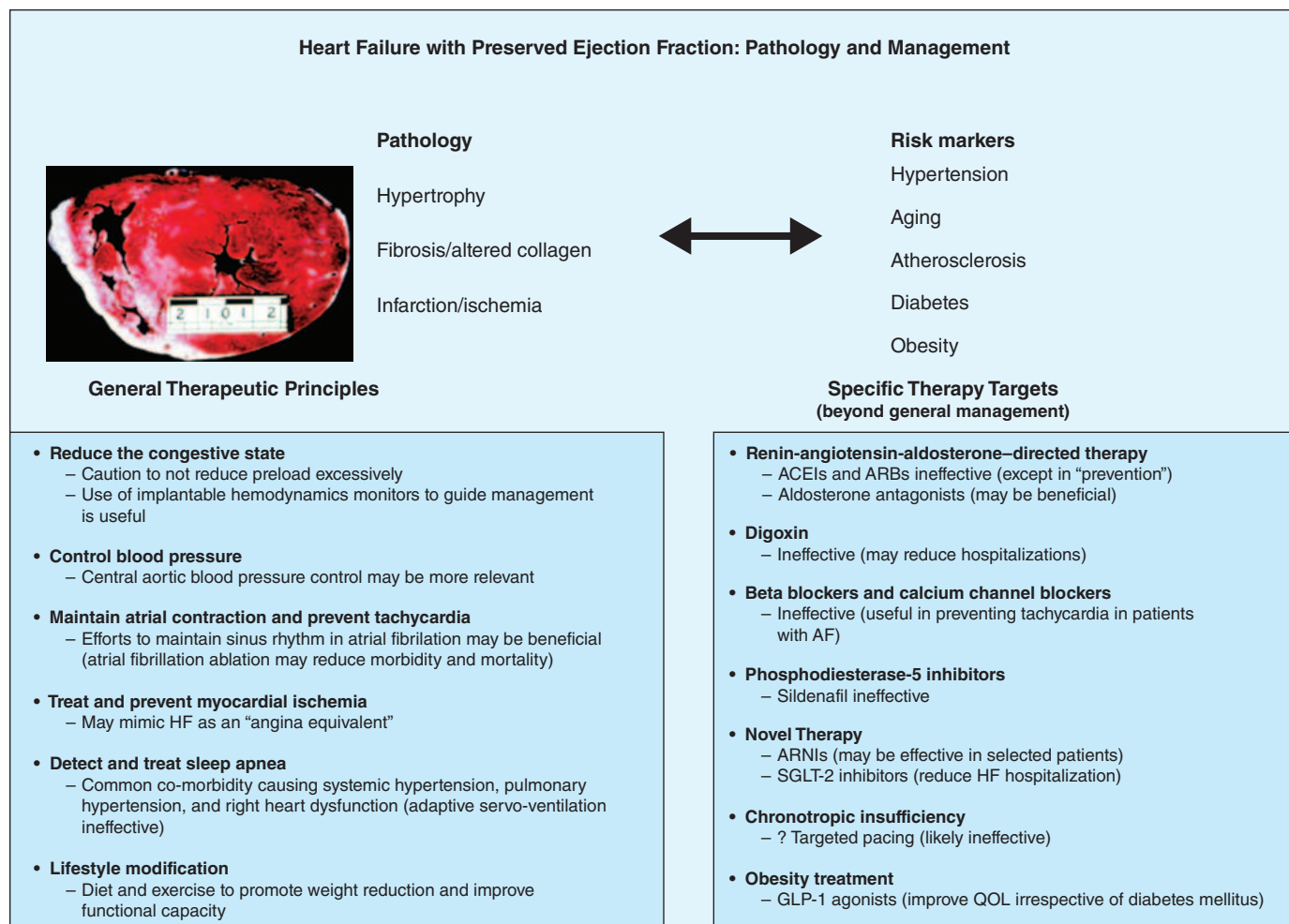


FIGURE 265-1 Pathophysiologic correlations, general therapeutic principles, and results of specific “directed” therapy in heart failure (HF) with preserved ejection fraction. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter 2; QOL, quality of life.

primary statistical analysis ($p = .06$). Directional benefits in secondary endpoints including QOL, NYHA class, and renal function favoring sacubitril-valsartan support a possible modest benefit of neprilysin inhibition in this population, particularly among patients with lower (i.e., mildly reduced) EF and in women, subgroups who appeared to derive greater benefit. Based on these data, sacubitril-valsartan has recently been approved in the United States for treatment of symptomatic HF across the full spectrum of EF, with benefits acknowledged to be greatest in those with LVEF below normal. The PARAGLIDE-HF trial randomly assigned patients with HF and EF $>40\%$ within 30 days of a worsening HF event to treatment with sacubitril-valsartan or valsartan. Although those assigned to sacubitril-valsartan experienced greater reductions in N-terminal prohormone of brain natriuretic peptide (NTproBNP) at 8 weeks, clinical benefits were modest and appeared to be confined to those with EF $\leq 60\%$, suggesting this therapy may be most effective in that subgroup.

CLINICAL GUIDING PRINCIPLES

Beyond disease-modifying therapy, treatment of HFpEF should focus on decongestion, aggressive management of medical comorbidities, and relief of exacerbating factors. A careful diagnostic approach is critical, since patients with HF and a normal or near-normal LVEF compose a heterogeneous group that includes patients with infiltrative heart disease (amyloidosis, hemochromatosis, sarcoidosis), storage disease (Fabry’s disease, Gaucher’s disease), hypertrophic cardiomyopathy, pericardial disease, pulmonary arterial hypertension, valvular heart disease, and primary right ventricular failure who may require a different management approach. For those with true HFpEF, aggressive control of blood pressure to guideline-recommended targets and

relief of volume overload with diuretics are critical to symptom relief. Excessive decrease in preload with diuretics and vasodilators may lead to underfilling the ventricle and subsequent azotemia, hypotension, and syncope. For patients at risk for coronary heart disease, deliberate evaluation for ischemia and consideration of coronary revascularization may be important. Since clinical outcomes in HFpEF are worse in the setting of atrial fibrillation, aggressive rate control, anticoagulation, and early consideration of sinus rhythm restoration are important. Comorbidities such as obesity, obstructive lung disease, sleep apnea, chronic kidney disease, and anemia/iron deficiency are increasingly recognized as important contributors to diminished functional capacity and QOL in patients with HFpEF and may be additional targets for therapy. Some investigators have suggested that the exercise intolerance in HFpEF is a manifestation of chronotropic insufficiency. While this hypothesis appears to be supported by small trials randomized trials of beta blocker withdrawal, improving chronotropic response through rate-adaptive atrial pacing did not improve functional capacity in the randomized RAPID-HF trial (Fig. 265-1).

ACUTE DECOMPENSATED HEART FAILURE

GENERAL PRINCIPLES

ADHF is a heterogeneous clinical syndrome most often resulting in need for hospitalization due to confluence of interrelated abnormalities of decreased cardiac performance, renal dysfunction, and alterations in vascular compliance. Admission with a diagnosis of ADHF is associated with excessive morbidity and mortality, with nearly half of these patients readmitted for management within 6 months, and a high short-term (5% in-hospital) and long-term cardiovascular mortality

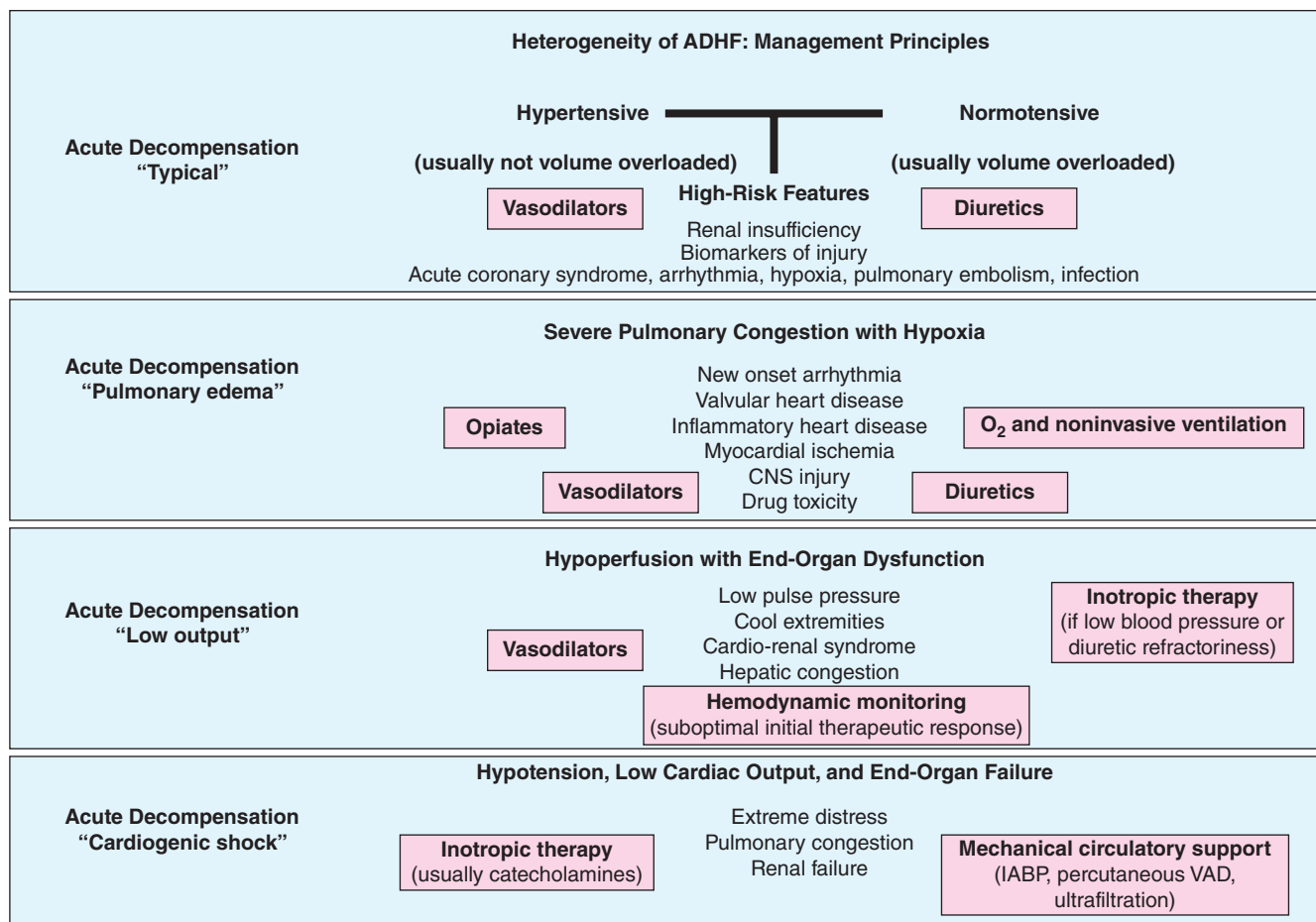


FIGURE 265-2 The distinctive phenotypes of acute decompensated heart failure (ADHF), their presentations, and suggested therapeutic routes. (Unique causes of ADHF, such as isolated right heart failure and pericardial disease, and rare causes, such as aortic and coronary dissection or ruptured valve structures or sinuses of Valsalva, are not delineated and are covered elsewhere.) CNS, central nervous system; IABP, intraaortic balloon pump; VAD, ventricular assist device.

(20% at 1 year). Importantly, long-term outcomes remain poor, with a combined incidence of cardiovascular deaths, HF hospitalizations, myocardial infarction, strokes, or sudden death reaching 50% at 12 months after hospitalization. The management of these patients remains difficult and principally revolves around volume control and hemodynamic optimization to maximize end-organ perfusion.

The first principle of management in ADHF is to identify and address the factors that precipitated decompensation. Important historical factors to consider are nonadherence to medications, dietary salt indiscretion, and usage of medications (including over-the-counter preparations) that may exacerbate HF, including nonsteroidal anti-inflammatory drugs, thiazolidinediones, tumor necrosis factor inhibitors, selected antidepressants, selected cancer therapies, cold and flu preparations with cardiac stimulants, and some herbal preparations. Coronary ischemia frequently drives HF exacerbation in patients with atherosclerotic cardiovascular disease and should be systematically investigated (either invasively or noninvasively) in all patients at risk to identify candidates for revascularization. Atrial and ventricular arrhythmias are common contributors to HF exacerbation and may trigger the need for antiarrhythmic drug suppression, cardioversion, or catheter ablation. Valvular heart disease is increasingly recognized as a target for therapy in patients with recurrent HF exacerbations and can be readily identified through echocardiography. Systemic infection and pulmonary thromboembolism are additional triggers of HF decompensation and should be routinely considered.

Concurrent with the identification of HF precipitants, effective management of ADHF requires pharmacologic therapy directed at hemodynamic optimization, including relief of congestion, reduction in afterload, and maximization of vital organ perfusion. The routine use of a pulmonary artery catheter is not recommended and should be restricted to those who present with features typical of low-output HF

or cardiogenic shock who may require vasopressor or mechanical circulatory support, those who are resistant or refractory to diuretic therapy, those with combined cardiorenal dysfunction in whom therapeutic goals are difficult to define at the bedside, and those with known or suspected pulmonary arterial hypertension in whom vasodilator therapy may be appropriate. Analysis of in-hospital registries has identified several parameters associated with worse outcomes: a blood urea nitrogen level >43 mg/dL (to convert to mmol/L, multiply by 0.357), systolic blood pressure <115 mmHg, a serum creatinine level >2.75 mg/dL (to convert to $\mu\text{mol/L}$, multiply by 88.4), and elevated cardiac biomarkers including natriuretic peptides and cardiac troponins. A useful clinical schema to identify treatment targets for the various phenotypic presentations and management goals in ADHF is depicted in [Fig. 265-2](#).

VOLUME MANAGEMENT

Intravenous Diuretic Agents Intravenous loop diuretic agents rapidly and effectively relieve symptoms of congestion and are essential when oral drug absorption is impaired. When high doses of diuretic agents are required or when the effect of bolus dosing is suboptimal, a continuous infusion may be needed to reduce toxicity and maintain stable serum drug levels. Randomized clinical trials of high- versus low-dose and bolus versus continuous infusion diuresis have not provided clear justification for the best diuretic strategy in ADHF, and as such, the use of diuretic regimens remains an art rather than science. For those refractory to loop diuretic treatment alone, addition of a thiazide diuretic agent such as chlorothiazide or metolazone to provide sequential nephron blockade may enhance natriuresis and facilitate decongestion, but also increases the risk of significant hypokalemia. Addition of acetazolamide to loop diuretic therapy in the randomized ADVOR trial was demonstrated to facilitate greater decongestion but was not associated with reduction in HF readmissions or mortality.

Change in weight is often used as a surrogate for adequate diuresis, but this objective measure of volume status may be surprisingly difficult to interpret, and weight loss during hospitalization does not necessarily correlate closely with outcomes. Effective decongestion may also be confirmed by improvement in clinical symptoms as well as the bedside examination documenting normalization of the jugular venous pressure, clearance of pulmonary rales, suppression of cardiac gallops, and resolution of peripheral edema, hepatomegaly, and abdominal ascites. It is generally advisable to continue diuresis until euvolemia has been achieved, since residual congestion or volume overload is strongly associated with risk for recurrent decompensation. PredischARGE measurement of natriuretic peptide levels, which are highly correlated with risk for postdischarge mortality and readmission, may also be useful in assessing the adequacy of therapy and stratifying risk. Chronic oral loop diuretic therapy is appropriate at discharge for most patients to maintain decongestion. The TRANSFORM-HF trial did not demonstrate any mortality or morbidity advantage of torsemide compared to furosemide for this purpose despite its greater oral bioavailability, longer half-life, and other potential beneficial effects on myocardial fibrosis, aldosterone production, sympathetic activation, ventricular remodeling, and natriuretic peptides noted in small studies.

The Cardiorenal Syndrome The cardiorenal syndrome is increasingly being recognized as a complication of ADHF. Multiple definitions have been proposed for the cardiorenal syndrome, but at its simplest, it can be thought to reflect the interplay between abnormalities of heart and kidney function, with deteriorating function of one organ while therapy is administered to preserve the other. Approximately 30% of patients hospitalized with ADHF exhibit abnormal renal function at baseline, and this is associated with longer hospitalizations and increased mortality. However, mechanistic studies have been largely unable to find correlation between deterioration in renal function, cardiac output, left-sided filling pressures, and reduced renal perfusion; most patients with cardiorenal syndrome demonstrate a preserved cardiac output. It is hypothesized that in patients with established HF, this syndrome represents a complex interplay of neurohormonal factors, potentially exacerbated by “backward failure” resulting from increased intraabdominal pressure and impairment in return of renal venous blood flow. Continued use of diuretic therapy may be associated with a reduction in glomerular filtration rate and a worsening of the cardiorenal syndrome when right-sided filling pressures remain elevated. In patients in the late stages of disease characterized by profound low cardiac output state, inotropic therapy or mechanical circulatory support has been shown to preserve or improve renal function in selected individuals in the short term until more definitive therapy such as assisted circulation or cardiac transplantation is implemented.

Ultrafiltration Ultrafiltration (UF) is an invasive fluid removal technique that may supplement the need for diuretic therapy. Proposed benefits of UF include controlled rates of fluid removal, neutral effects on serum electrolytes, and decreased neurohormonal activity. This technique has also been referred to as aquapheresis in recognition of its electrolyte depletion-sparing effects. In an initial study evaluating UF versus conventional therapy, fluid removal was improved, and subsequent HF hospitalizations and urgent clinic visits were reduced with UF; however, no improvement in renal function and no subjective differences in dyspnea scores or adverse outcomes were noted. In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, 188 patients with ADHF and worsening renal failure were randomized to stepped pharmacologic care or UF. The primary endpoint was a change in serum creatinine and change in weight (reflecting fluid removal) at 96 h. Although similar weight loss occurred in both groups (~5.5 kg), there was a rise in serum creatinine among patients allocated to the UF group. Deaths and hospitalizations for HF were no different between groups, but there were more adverse events in the UF group, mainly due to kidney failure, bleeding complications, and intravenous catheter-related complications. This investigation argues against using UF as a primary strategy in patients with ADHF who are diuretic-responsive. Whether UF is useful as a rescue strategy in diuretic refractory patients with advanced renal disease

remains an open question, and this strategy continues to be employed judiciously in such situations.

■ VASOACTIVE THERAPY

Vasodilators including *intravenous nitroglycerin*, *sodium nitroprusside*, and *nesiritide* (a recombinant brain-type natriuretic peptide) are frequently used in ADHF to lower intracardiac filling pressures and reduce systemic vascular tone. Rapid reduction in ventricular preload and afterload with these therapies may be effective in providing symptom relief in patients with pulmonary edema and in restoring end-organ perfusion for those with low cardiac output and high systemic vascular resistance. Nitroglycerine principally impacts venous tone and ventricular preload, whereas sodium nitroprusside is a potent arterial and venous vasodilator with more comprehensive effects on both preload and afterload. While intravenous nitroglycerine is commonly utilized as an adjunct to diuretics for acute management of symptomatic HF and pulmonary edema, nitroprusside is typically reserved for use in those with adequate arterial pressure or invasive hemodynamic monitoring due to the risk for hypotension. The hemodynamic effects of nesiritide are intermediate between those of nitroglycerine and nitroprusside, with head-to-head comparisons with nitroglycerine suggesting more rapid reduction in pulmonary capillary wedge pressure and pulmonary vascular resistance. Clinical utilization of nesiritide has waned due to concerns raised regarding heightened risks of renal insufficiency and mortality identified in early trials. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) randomizing 7141 patients with ADHF to nesiritide or placebo did not confirm this risk but identified no clear clinical benefit regarding subsequent HF admissions, mortality, or symptom relief (reduction in dyspnea). Renal function did not worsen, but increased rates of hypotension were noted. A smaller study of low-dose nesiritide in acute HF (Renal Optimization Strategies Evaluation Acute Heart Failure Study [ROSE-AHF]) also showed no incremental benefit over intravenous diuretics for relief of congestion or preservation of renal function. Despite apparent safety in ADHF, the routine use of nesiritide is accordingly not recommended.

Other novel vasodilators have been explored for the management of ADHF. Recombinant human relaxin-2, or *serelaxin*, is a vasodilatory hormone known to contribute to cardiovascular and renal adaptations during pregnancy. In the Relaxin in Acute Heart Failure (RELAX-AHF) trial, 1161 patients hospitalized with ADHF, evidence of congestion, and systolic pressure >125 mmHg were randomized to treatment with serelaxin or placebo in addition to standard HF therapy. Serelaxin improved dyspnea, reduced signs and symptoms of congestion, and was associated with less early worsening of HF. A positive signal of reduced mortality identified in an exploratory analysis prompted a second study (RELAX-AHF2), which did not confirm an effect on cardiovascular death or worsening HF. Accordingly, this agent was not approved for use in clinical practice.

One hypothesis for the failure of vasodilator therapies to improve clinical outcomes in ADHF despite favorable hemodynamic effects is related to the acute injury hypothesis; in this model, acute HF is analogous to presentation with an acute coronary syndrome, with the initial hours of presentation representing a period of vulnerability to myocardial damage (reflected in a rise in markers of myocyte injury such as cardiac troponins) as a consequence of abrupt increases in ventricular wall stress related to acute plasma volume expansion. To test this hypothesis, the Trial of Ularitide Safety and Efficacy in Acute Heart Failure (TRUE-AHF) randomly allocated 2157 patients with acute HF to early treatment with the synthetic natriuretic peptide *ularitide* (at a dose sufficient to reduce ventricular wall stress) or placebo. Despite a very short duration between initial clinical presentation and pharmacologic intervention (<6 h) and early hemodynamic benefits, no improvement in clinical outcomes was observed in patients allocated to ularitide at 6 months. Ularitide was associated with a higher rate of hypotension and worsening serum creatinine. These data undermine the notion that acute myocardial damage related to ventricular distension associated with HF exacerbation drives subsequent clinical outcomes and argue against the clinical importance of early vasodilator therapy in ADHF.

■ INOTROPIC THERAPY

Impairment of myocardial contractility often accompanies ADHF, and pharmacologic agents that increase intracellular concentration of cyclic adenosine monophosphate via direct or indirect pathways, such as sympathomimetic amines (*dopamine*, *dobutamine*) and phosphodiesterase-3 inhibitors (*milrinone*), respectively, serve as positive inotropic agents. Their activity leads to an increase in cytoplasmic calcium. Inotropic therapy in those with a low-output state augments cardiac output, reduces systemic vascular resistance, improves perfusion, and relieves congestion acutely. Although systematic head-to-head comparisons are available to identify a “best” agent, slight variations in the hemodynamic effects of inotropic drugs may condition selection of the appropriate drug for a given clinical context. Dopamine exhibits dose-dependent effects on dopaminergic, α -, and β -adrenergic receptors, with vasodilatory effects predominating at lower doses ($<2 \mu\text{g/kg}$ per min), β -adrenergic (inotropic) effects at moderate doses, and α -adrenergic effects (vasoconstriction) at higher doses (typically $>10 \mu\text{g/kg}$ per min). Low-dose (“renal dose”) dopamine has been explored as an adjunctive strategy for preservation of renal function and augmentation of diuresis in acute HF but does not appear to provide incremental advantage over routine therapy with intravenous diuretics (ROSE-AHF).

Milrinone is typically associated with a greater reduction in systemic and pulmonary vascular resistance than dobutamine and, accordingly, carries a higher risk of systemic hypotension. Moreover, because milrinone has a longer half-life and is renally excreted, it requires dose adjustments in the setting of kidney dysfunction. Because milrinone acts downstream from the β_1 -adrenergic receptor, it may provide an advantage in patients receiving beta blockers when admitted to the hospital.

Long-term inotropic therapy is associated with a heightened risk of mortality in HF, perhaps due to the increased risk of arrhythmia and sudden death. Routine, short-term use of milrinone in patients hospitalized with ADHF in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial was associated with increased risk of atrial arrhythmias and prolonged hypotension, but no benefit regarding subsequent mortality or HF hospitalization. Accordingly, routine use of inotropic support in ADHF is discouraged, and these agents are currently indicated principally for short-term use as bridge therapy (to either left ventricular assist device support or to transplant) in cardiogenic shock or as selectively applied palliation in end-stage HF.

Novel inotropic agents that leverage the concept of myofilament calcium sensitization rather than increasing intracellular calcium levels have been introduced. *Levosimendan* is a calcium sensitizer that provides inotropic activity but also possesses phosphodiesterase-3 inhibition properties that are vasodilatory. Two trials, the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) and Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), have tested this agent in ADHF. SURVIVE compared levosimendan with dobutamine, and despite an initial reduction in circulating B-type natriuretic peptide levels in the levosimendan group compared with patients in the dobutamine group, this drug did not reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. The second trial compared levosimendan against traditional noninotropic therapy and found a modest improvement in symptoms with worsened short-term mortality and ventricular arrhythmias. Although levosimendan has been approved for use to support management of HF in several countries worldwide, it is not approved for use in the United States, largely owing to the lack of compelling data for incremental efficacy in comparison with conventional inotropic drugs or standard HF therapies.

(Table 265-1 depicts typical inotropic, vasodilator, and diuretic drugs used in ADHF.)

■ OTHER THERAPIES FOR ADHF

Other trials testing unique agents have yielded disappointing results in the situation of ADHF. Adenosine has been implicated as a mediator of worsening renal function and diuretic resistance, and accordingly, treatment with *adenosine receptor antagonists* was postulated to be

potentially beneficial in relieving symptoms and preserving renal function in patients with acute HF. Among patients with acute HF and renal dysfunction enrolled in the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial, no cardiovascular or renal benefit was observed. Similarly, despite compelling theoretical benefit of vasopressin receptor antagonism in acute HF (based on the central role of vasopressin in mediating the fluid retention that contributes to worsening HF), no benefit of the oral selective vasopressin-2 antagonist *tolvaptan* was seen regarding mortality or HF-associated morbidity in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial.

■ CLINICAL GUIDING PRINCIPLES

In the absence of data to support specific pharmacologic interventions in ADHF, management is largely goal-directed and focused on decongestion to relieve symptoms, investigation and suppression of triggers for recurrent decompensation, and careful transition to longitudinal HF management. Patients who fail to respond adequately to medical therapy or who develop hemodynamic instability may benefit from pulmonary artery catheter placement to guide titration of vasoactive therapy or inotropic support; in those with hemodynamics suggestive of cardiogenic shock, mechanical assist devices may be required (Chap. 271). Following stabilization, all patients should receive education regarding HF self-management prior to discharge, including guidance regarding diet and lifestyle modification, identification of worsening HF symptoms, and whom to contact in the event of clinical deterioration. Early postdischarge follow-up of patients following hospitalization for management of worsening HF is associated with lower rates of hospital readmission. For patients with HFrEF hospitalized with ADHF, data suggest that institution of appropriate guideline-directed medical therapy prior to hospital discharge is associated with higher rates of adherence to appropriate pharmacologic treatment in longitudinal follow-up and may be associated with improved outcomes in the early postdischarge interval. In the Comparison of Sacubitril-Valsartan Versus Enalapril on Effect on NTproBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) study of patients with HFrEF stabilized after hospital admission for ADHF, predischARGE initiation of sacubitril-valsartan compared with enalapril was associated with greater reductions in natriuretic peptides as well as lower rates of composite death and HF readmission at 8 weeks. Similarly, in the EMPULSE trial, predischARGE initiation of the SGLT-2 inhibitor empagliflozin in hospitalized HF patients across the spectrum of EF was associated with reductions in a hierarchical clinical composite outcome at 90 days. More recently, in the STRONG-HF trial, an intensive postdischarge treatment strategy of frequent follow-up and rapid uptitration of guideline-recommended medical therapy was associated with lower rates of death and HF readmission at 180 days compared with usual care. These results were consistent in those with EF $\leq 40\%$ and those with EF $>40\%$, underscoring the need for early postdischarge follow-up and medical optimization in high-risk patients following a worsening HF event, regardless of EF.

HEART FAILURE WITH REDUCED EJECTION FRACTION

The past 50 years have witnessed great strides in the management of HFrEF. Treatment of symptomatic HF has evolved from a renocentric (diuretics) and hemodynamic therapy model (digoxin, inotropic therapy) to an era of disease-modifying therapy with neurohormonal antagonism. In this regard, RAAS blockers (including ARNIs), β -adrenergic receptor blockers, and, most recently, SGLT-2 inhibitors form pillars of pharmacotherapy and facilitate stabilization and even improvement in cardiac structure and function with consequent reduction in symptoms, improvement in QOL, decreased burden of hospitalizations, and a decline in mortality from both pump failure and arrhythmic deaths (Fig. 265-3).

TABLE 265-1 Vasoactive Therapy in Acute Decompensated Heart Failure

DRUG CLASS	GENERIC DRUG	USUAL DOSING	SPECIAL CAUTION	COMMENTS
Inotropic therapy				Use in hypotension, end-organ hypoperfusion, or shock states
	Dobutamine	2–20 µg/kg per min	Increased myocardial oxygen demand, arrhythmia	Short acting, an advantage; variable efficacy in presence of beta blockers (requires higher doses); clinical tolerance to prolonged infusions; concerns with hypersensitivity carditis (rare)
	Milrinone	0.375–0.75 µg/kg per min	Hypotension, arrhythmia	Decrease dose in renal insufficiency; avoid initial bolus; effectiveness retained in presence of beta blockers
	Levosimendan	0.1 µg/kg per min; range, 0.05–0.2 µg/kg per min	Hypotension, arrhythmia	Long acting; should not be used in presence of low blood pressure; similar effectiveness as dobutamine but effectiveness retained in presence of beta blockers
Vasodilators				Use in presence of pulmonary congestion for rapid relief of dyspnea, in presence of a preserved blood pressure
	Nitroglycerin	10–20 µg/min, increase up to 200 µg/min	Headache, flushing, tolerance	Most common vasodilator but often underdosed; effective in higher doses
	Nesiritide	Bolus 2 µg/kg and infusion at 0.01 µg/kg per min	Hypotension	Decrease in blood pressure may reduce renal perfusion pressure; bolus may be avoided since it increases hypotension predilection
	Nitroprusside	0.3 µg/kg per min titrated to 5 µg/kg per min	Thiocyanate toxicity in renal insufficiency (>72 h)	Requires arterial line placement for titration for precise blood pressure management and prevention of hypotension
	Serelaxin	N/A (tested at 30 µg/kg per d)	Baseline blood pressure should be >125 mmHg	Not widely commercially available; ineffective in confirmatory trials
	Ularitide	15 ng/kg per min (48 h)	Baseline blood pressure >116 mmHg	Excess hypotension and increased serum creatinine
Diuretics				First line of therapy in volume overload with congestion; may use bolus or continuous dosing; initial low dose (1 × home dose) or high dose (2.5 × home dose) equally effective with higher risk of renal worsening with higher dose
	Furosemide	20–240 mg daily	Monitor for electrolyte loss	In severe congestion, use intravenously and consider continuous infusion (not trial supported)
	Torsemide	10–100 mg daily	Monitor for electrolyte loss	High bioavailability, can be given orally; anecdotally more effective in advanced heart failure states if furosemide less bioavailable (due to gut congestion)
	Bumetanide	0.5–5 mg daily	Monitor for electrolyte loss	Can be used orally; intermediate bioavailability
	Adjuvant diuretics for augmentation	N/A	Metolazone, chlorthalidone, spironolactone, acetazolamide	Acetazolamide is useful in presence of alkalosis (bicarbonate level >27mEq/L); metolazone given in 2.5- to 10-mg doses; concomitant use of loop diuretics and thiazides associated with risk for severe hypokalemia, careful laboratory monitoring advised; spironolactone is useful in presence of severe hypokalemia and normal renal function

Abbreviation: N/A, not applicable.

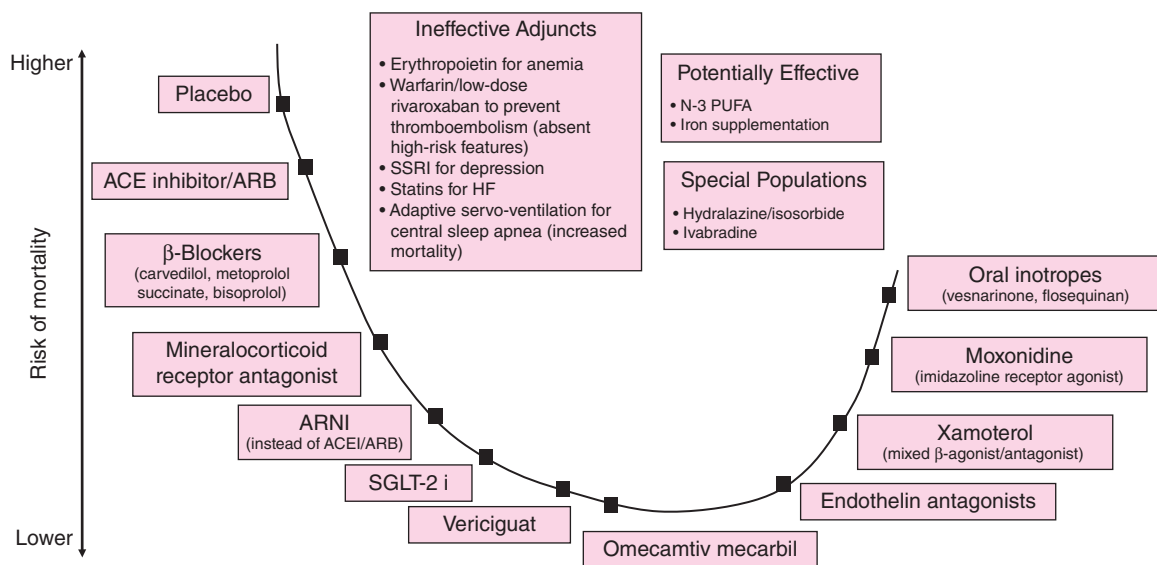


FIGURE 265-3 Progressive decline in mortality with angiotensin-converting enzyme (ACE) inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), beta blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and balanced vasodilators (*selected populations such as African Americans). Addition of selected therapies (ivabradine, vericiguat) may further reduce heart failure (HF) hospitalization but does not substantially impact mortality. Further stack-on neurohormonal therapy is ineffective or results in worse outcome. Management of comorbidity (e.g., iron deficiency, sleep apnea) is of unproven efficacy. HFrEF, heart failure with reduced ejection fraction; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibitor.

■ NEUROHORMONAL ANTAGONISM

Meta-analyses suggest a 23% reduction in mortality and a 35% reduction in the combined endpoint of mortality and hospitalizations for HF in patients with symptomatic HFrEF treated with ACE inhibitors (ACEIs). Addition of β -adrenergic receptor blockers to background therapy with ACEIs provides a further 35% reduction in mortality. Although placebo-controlled studies are lacking, several noninferiority trials have demonstrated comparable efficacy of ARBs and ACEIs in patients with HFrEF, making ARBs a suitable alternative for patients who are intolerant to ACEIs due to cough or angioedema. Abundant data support the efficacy across the full spectrum of HF severity (including those with NYHA class III–IV functional capacity), as well as the safety data of these agents. These observations demonstrate the basis for the tolerability of these agents even in subgroups at higher risk for adverse effects such as those with mild-moderate chronic kidney disease. In diabetes mellitus and chronic obstructive lung disease, these agents have been established as foundational therapy for HFrEF as directed by consensus guidelines. Both agents are generally recommended for all patients with HFrEF, independent of symptom burden, and should be titrated to the doses proven to provide clinical benefit or to the maximally tolerated dose. The inability to tolerate initiation or dose titration of neurohumoral antagonists due to hypotension, worsening HF, or progressive renal insufficiency is a poor prognostic marker and may be a cardinal manifestation of transition to an advanced HF phenotype.

Class Effect and Sequence of Administration ACEIs and ARBs exert their beneficial effects in HFrEF as a class; however, the beneficial effects of beta blockers are thought to be limited to specific drugs. Beta blockers with intrinsic sympathomimetic activity (xamoterol) and other agents, including bucindolol, have not demonstrated a survival benefit. Based on the available data, beta blocker use in HFrEF should ideally be restricted to carvedilol, bisoprolol, and metoprolol succinate—agents tested and proven to improve survival in clinical trials. Whether beta blockers or ACEIs should be started first was answered by the Cardiac Insufficiency Bisoprolol Study (CIBIS) III, in which outcomes did not vary based on the sequence of drug initiation. Thus, it matters little which agent is initiated first; what does matter is that optimally titrated doses of both ACEIs and beta blockers be established in a timely manner.

Dose and Outcome In general, the benefits of neurohumoral antagonists in HFrEF are closely related to the dose achieved, girding the rationale for aggressive titration to target doses as defined by clinical trials. Prospective trials of high- versus low-dose ACEIs (ATLAS), ARBs (HEAAL), and beta blockers (MOCHA) consistently favor the higher dose, with lower rates of death and HF hospitalization seen in the higher-dose group. Clinical experience suggests that, in the absence of symptoms to suggest hypotension (fatigue and dizziness), pharmacotherapy may be uptitrated every 2 weeks in stable ambulatory patients as tolerated. Notably, data from large registries in the United States and Europe suggest that guideline-directed medical therapy for patients with HFrEF is frequently underutilized and underdosed, leaving considerable room for quality improvement.

■ MINERALOCORTICOID RECEPTOR ANTAGONISTS

Addition of mineralocorticoid receptor antagonists to treatment with ACEI/ARBs and beta blockers in patients with symptomatic HFrEF (NYHA class II–IV) is associated with further reductions in morbidity and mortality. Elevated aldosterone levels in HFrEF promote sodium retention, electrolyte imbalance, and endothelial dysfunction and may directly contribute to myocardial fibrosis. Hyperkalemia and worsening renal function are concerns, especially in patients with underlying chronic kidney disease, and renal function and serum potassium levels must be closely monitored. Spironolactone is the most utilized agent in this class based on efficacy demonstrated in the Randomized Aldactone Evaluation Study (RALES) in patients with HFrEF and NYHA class III–IV symptoms. Eplerenone (studied principally in patients with milder NYHA class II symptoms and those with HF or

left ventricular dysfunction complication myocardial infarction) lacks the antiandrogen effects of spironolactone and may be a suitable alternative for patients who experience sexual side effects (gynecomastia, erectile dysfunction, diminished libido).

■ RAAS THERAPY AND NEUROHORMONAL “ESCAPE”

Since angiotensin II can be generated by non-ACE pathways, levels of angiotensin II may recover to pretreatment levels during long-term ACEI therapy. This phenomenon of neurohormonal “escape” has fueled interest in dual blockade of the RAAS using ACEI and ARBs in combination. In both the Valsartan Heart Failure Trial (Val-HeFT) and the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM-Added) trial, addition of an ARB to an ACEI and other HF therapy was associated with a lower risk of HF hospitalizations. Since neither trial mandated an evidence-based dose of an ACEI, it remains unclear whether combination therapy was clearly superior to a strategy of maximizing a single agent through dose titration. Subsequent data from the Valsartan in Acute Myocardial Infarction (VALIANT) trial suggested that the addition of the ARB valsartan to an evidence-based dose of the ACEI captopril in patients with HF complicating myocardial infarction was associated with an increase in adverse events without any added benefit compared with monotherapy for either group. The findings of the VALIANT trial are also informed by the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE), which randomly allocated 7016 patients with HFrEF to treatment with enalapril (targeted dose 10 mg twice daily as recommended by guidelines), the plasma renin inhibitor aliskiren, or the combination on top of standard HF therapy. In that study, combination treatment with aliskiren and enalapril was associated with higher rates of hyperkalemia, hypotension, and worsening renal function, but no incremental benefit regarding HF hospitalization or cardiovascular mortality. Together, these data argue for a ceiling of benefit of angiotensin inhibition in HFrEF, beyond which further inhibition brings more adverse effects without additional efficacy. Guidelines discourage the combination of an ACEI, ARB, and spironolactone in HFrEF due to the risks of hyperkalemia and renal dysfunction, and for patients, treatment with either an ACEI or ARB and spironolactone is deemed most appropriate.

■ ALTERNATIVE VASODILATORS

The combination of hydralazine and nitrates has been demonstrated to improve survival in HFrEF. Hydralazine reduces systemic vascular resistance and induces arterial vasodilatation by affecting intracellular calcium kinetics; nitrates are transformed in smooth muscle cells into NO, which stimulates cyclic guanosine monophosphate production and consequent arterial-venous vasodilation. This combination improves survival but to a lesser extent than ACEIs. However, in individuals with HFrEF unable to tolerate RAAS-based therapy for reasons such as renal insufficiency or hyperkalemia, this combination is preferred as a disease-modifying approach. A trial conducted in self-identified African Americans, the African-American Heart Failure Trial (A-HeFT), studied a fixed dose of isosorbide dinitrate with hydralazine in patients with advanced symptoms of HFrEF who were receiving standard background therapy including an ACEI and beta blocker. The study demonstrated improvements in survival and hospital admission for HF in the treatment group. Adherence to this regimen is limited by the thrice-daily dosing schedule.

■ NOVEL NEUROHORMONAL ANTAGONISTS

Despite an abundance of animal and clinical data demonstrating deleterious effects of activated neurohormonal pathways beyond the RAAS and sympathetic nervous system, targeting such pathways with incremental blockade has been largely unsuccessful. As an example, the endothelin antagonist bosentan is associated with worsening HF in HFrEF despite demonstrating benefits in right-sided HF due to pulmonary arterial hypertension. Similarly, the centrally acting sympatholytic agent moxonidine worsens outcomes in left HF. The combined drug omapatrilat hybridizes an ACEI with a neutral endopeptidase (neprilysin) inhibitor, and this agent was tested in the Omapatrilat

TABLE 265-2 Guideline-Directed Pharmacologic Therapy and Target Doses in Heart Failure with Reduced Ejection Fraction

DRUG CLASS	GENERIC DRUG	MEAN DAILY DOSE IN CLINICAL TRIALS (mg)	INITIATION (mg)	TARGET DOSE (mg)
Angiotensin-Converting Enzyme Inhibitors				
	Lisinopril	4.5–33	2.5–5 qd	20–35 qd
	Enalapril	17	2.5 bid	10–20 bid
	Captopril	123	6.25 tid	50 tid
	Trandolapril	N/A	0.5–1 qd	4 qd
Angiotensin Receptor Blockers				
	Losartan	129	50 qd	150 qd
	Valsartan	254	40 bid	160 bid
	Candesartan	24	4–8 qd	32 qd
Aldosterone Antagonists				
	Eplerenone	42.6	25 qd	50 qd
	Spironolactone	26	12.5–25 qd	25–50 qd
Beta Blockers				
	Metoprolol succinate CR/XL	159	12.5–25 qd	200 qd
	Carvedilol	37	3.125 bid	25–50 bid
	Bisoprolol	8.6	1.25 qd	10 qd
Arteriovenous Vasodilators				
	Hydralazine isosorbide dinitrate	270/136	37.5/20 tid	75/40 tid
	Fixed-dose hydralazine/isosorbide dinitrate	143/76	37.5/20 qid	75/40 qid
Angiotensin Receptor–Neprilysin Inhibitor				
	Sacubitril-valsartan	375	100 bid	200 bid
SGLT-2 Inhibitor				
	Dapagliflozin	10	10 qd	10 qd
	Empagliflozin	10	10 qd	10 qd
	Sotagliflozin	200	200 qd	200 qd
Novel Therapies				
	Vericiguat (sGC stimulator)	9.2	2.5 qd	10 qd
	Omecamtiv mecarbil (myosin activator)	Not reported	25 bid	Up to 50 mg bid (based on plasma concentrations)

Abbreviations: sGC, soluble guanylyl cyclase; SGLT-2, sodium-glucose cotransporter 2.

Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial. This drug did not favorably influence the primary outcome measure of the combined risk of death or hospitalization for HF requiring intravenous treatment compared with enalapril alone, and notably, the risk of angioedema was increased in patients assigned to omapatrilat.

The risk of angioedema with composite ACE/neprilysin inhibition appears to be related to excessive blockade of bradykinin breakdown by this combination. Blockade of angiotensin at the receptor level with an ARB leaves the ACE pathway for bradykinin breakdown intact and is associated with lower angioedema risk. Recently, a composite ARNI, sacubitril-valsartan (formerly LCZ696), was developed and applied to the treatment of patients with HFrEF. In the PARADIGM-HF trial, 8399 patients with HFrEF treated with guideline-directed medical therapy were randomly allocated to treatment with either enalapril or sacubitril-valsartan after a run-in period designed to ensure tolerability of both drugs at target doses. Compared to those assigned to enalapril, patients assigned to sacubitril-valsartan experienced a dramatic 20% reduction in the composite primary endpoint of cardiovascular death or HF hospitalization and a 16% reduction in all-cause mortality, as well as clinically important improvements in QOL measures. Sacubitril-valsartan was well tolerated and associated with lower rates of hyperkalemia and worsening renal function, but greater rates of symptomatic hypotension, than enalapril. Guidelines now advocate a switch to ARNI for patients with symptomatic HFrEF who tolerate ACEIs and ARBs, and emerging data suggest that up-front utilization of ARNI in patients with de novo HF naïve to ACEIs/ARBs may also

be appropriate for those with adequate blood pressure to tolerate it. Given ongoing concern for angioedema, use of ARNI is contraindicated in patients with prior history of angioedema, and those being transitioned from ACEIs should receive ARNI only after a 36-h gap to limit the risk of overlap. **Table 265-2** lists the common neurohormonal and vasodilator regimens for HFrEF.

HEART RATE MODIFICATION

Distinct from β -adrenergic receptor blockers, ivabradine, an inhibitor of the I_f current in the sinoatrial node, selectively reduces heart rate without affecting cardiac contractility or vascular tone. The Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial (SHIFT) was conducted in patients with NYHA class II or III HFrEF, prior HF hospitalization, sinus rhythm, and heart rate >70 beats/min. Ivabradine reduced the combined endpoint of cardiovascular-related death and HF hospitalization in proportion to the degree of heart rate reduction, which supports the notion that heart rate may be a therapeutic target in patients with HFrEF in sinus rhythm. Importantly, despite a protocol requirement for patients to be treated with a maximally tolerated dose of a beta blocker prior to study entry, 10% of patients randomized were not treated with a beta blocker, and 75% were treated at subtarget doses. Accordingly, it remains unclear whether this agent would have been effective in patients receiving robust, guideline-recommended therapy for HF; however, these data do support the potential value of ivabradine as an adjunct or alternative in those who are intolerant to initiation or dose titration of beta blockers. Clinical guidelines have been adapted

to encourage consideration of ivabradine in patients with HFrEF who remain symptomatic after treatment with guideline-based ACEI/ARB/ARNIs, beta blockers, and mineralocorticoid receptor antagonists; are in sinus rhythm; and have a residual heart rate >70 beats/min.

■ SGLT-2 INHIBITION

Inhibitors of SGLT-2 have been shown to reduce cardiovascular events and mortality among patients with type 2 diabetes mellitus at high cardiovascular risk or with established atherosclerotic cardiovascular disease. A particular signal of benefit has been seen regarding the incidence of HF hospitalization, which was reduced by 35% in comparison to placebo in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOMES) study. Because the cardiovascular benefits of SGLT-2 inhibition appear to be unrelated to the degree of reduction in hemoglobin A_{1c}, it has been postulated that the HF benefits of this therapy might be extended to patients without diabetes mellitus. Recently, the Dapagliflozin in Heart Failure (DAPA-HF) study randomized 4744 patients with symptomatic HFrEF treated with guideline-directed medical therapy (including a beta blocker, ACEI/ARB/ARNI, and spironolactone in >70% of patients) to treatment with either the SGLT-2 inhibitor dapagliflozin (dosage 10 mg daily) or placebo over a median duration of follow-up of 18.2 months. Patients allocated to dapagliflozin experienced a highly significant 26% reduction in the primary composite endpoint of worsening HF or death from cardiovascular causes, an effect that was consistent in both patients with (42%) and without diabetes mellitus at baseline. These results have been reinforced by the results of the EMPEROR-Reduced trial, in which 3730 patients with symptomatic HF and EF of ≤40% were randomized to treatment with empagliflozin (dosage 10 mg once daily) or placebo in addition to recommended therapy. Over a median 16-month follow-up, patients allocated to empagliflozin experienced a 25% reduction in the primary composite endpoint of cardiovascular death or hospitalization for HF, an effect that was again consistent regardless of the presence or absence of diabetes mellitus. Together, these studies have driven consensus guidelines to consider use of SGLT-2 inhibitors as foundational therapy for HF alongside ARNIs, beta blockers, and mineralocorticoid receptor antagonists.

■ SOLUBLE GUANYLYL CYCLASE STIMULATION

Soluble guanylyl cyclase (sGC) is a key enzyme of the NO signaling pathway that catalyzes synthesis of cyclic guanosine monophosphate (GMP), producing vasodilation. Vericiguat is a novel oral sGC stimulator that enhances cyclic GMP and NO signaling by directly stimulating sGC and sensitizing sGC to endogenous NO. The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) randomly assigned 5050 patients with chronic HF, NYHA class II–IV symptoms, LVEF <45%, elevated natriuretic peptide levels, and evidence of worsening HF (requiring recent hospitalization or intravenous diuretic therapy) despite guideline-directed medical therapy to treatment with vericiguat (target dose 10 mg) or matching placebo over a median follow-up of 11 months. The primary study results were notable for a modest 10% relative risk reduction in the primary composite outcome of cardiovascular death or HF hospitalization among those assigned to vericiguat, an effect driven principally by effects on HF hospitalization, rather than cardiovascular death. As vericiguat was generally well tolerated with a low rate of serious adverse events, these data suggest a potential role for sGC stimulation as an adjunct to guideline-directed medical therapy in the high-risk group of HFrEF patients with recent congestive exacerbations requiring treatment, although these data await further review by regulatory agencies and guidelines committees.

■ MYOSIN ACTIVATION

A novel approach to augmentation of cardiac output is to prolong ventricular systole without increasing myocardial contractility. As a selective myosin activator, *omecamtiv mecarbil* prolongs the ejection period and increases fractional shortening without altering the force of contraction. This agent, distinct from inotropic agents, is not associated with an increase in myocardial oxygen demand. Importantly,

the drug is available for oral, rather than intravenous, administration, enabling chronic use in the ambulatory setting. In the COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trial of 448 patients with chronic HF and left ventricular systolic dysfunction, treatment with *omecamtiv mecarbil* for 20 weeks was associated with significant improvements in cardiac function and indices of left ventricular remodeling, as well as reductions in natriuretic peptide levels. Notably, the safety profile was comparable to placebo, with no increase in cardiac adverse events despite a modest increase in cardiac troponins in patients allocated to *omecamtiv mecarbil*. These promising preliminary data fueled a larger clinical outcomes trial (GALACTIC-HF), in which 8256 patients with symptomatic chronic HF and EF of ≤35% were randomized to treatment with *omecamtiv mecarbil* (25–50 mg twice daily based on plasma levels) or placebo in addition to standard HF therapy. Over a median follow-up of 21.8 months, patients allocated to *omecamtiv mecarbil* experienced a 14% reduction in the primary composite endpoint of death from cardiovascular causes or first HF event (hospitalization or urgent visit for HF), an outcome driven principally by reduction in HF events (no measurable effect on cardiovascular death alone). A possible signal of greater benefit in patients with features of advanced HF (lower EF, higher natriuretic peptide levels, more severe symptoms) combined with a favorable safety and tolerability profile suggests a possible role for this agent in patients with late-stage disease, although additional study is needed.

■ DIGOXIN

Digitalis glycosides exert a mild inotropic effect, attenuate carotid sinus baroreceptor activity, and are sympatho-inhibitory. These effects decrease serum norepinephrine levels, plasma renin levels, and possibly aldosterone levels. The Digitalis Investigation Group (DIG) trial demonstrated a reduction in HF hospitalizations in the treatment group (patients with HF and sinus rhythm) but no reduction in mortality or improvement in QOL. Importantly, treatment with digoxin resulted in a higher mortality rate and hospitalizations in women than men. It should be noted that low doses of digoxin are sufficient to achieve any potentially beneficial outcomes, and higher doses breach the therapeutic safety index. Although digoxin levels should be checked to minimize toxicity and although dose reductions are indicated for higher levels, no adjustment is made for low levels. Generally, digoxin is now relegated as late-line therapy for patients who remain profoundly symptomatic despite optimal neurohormonal blockade and adequate volume control.

■ ORAL DIURETICS

Neurohormonal activation results in avid salt and water retention. Diuretic therapy is typically required in patients with symptomatic HF to remedy congestive symptoms as a prelude to initiation and titration of neurohormonal therapy. Because of their potent effect on renal sodium excretion, loop diuretic agents are the preferred agents, with thiazide diuretics reserved for use in combination with loop diuretics for those with refractory volume overload. Frequent dose adjustments of loop diuretics may be necessary during longitudinal follow-up of patients with HF because of variable oral absorption and fluctuations in renal function. Patients who fail to respond to furosemide at high doses may benefit from transition to torsemide or bumetanide, which have greater oral bioavailability, but recent studies have not confirmed a greater benefit for alternatives to furosemide as a loop diuretic. Importantly, clinical trial data confirming efficacy are limited, and no data suggest that these agents improve survival. Since loop diuretics do enhance neurohumoral activation, dosing should be minimized as possible to maximize the balance of risk and benefit.

■ CALCIUM CHANNEL ANTAGONISTS

Amlodipine and felodipine, second-generation calcium channel-blocking agents, safely and effectively reduce blood pressure in HFrEF but do not affect morbidity, mortality, or QOL. The first-generation agents, including verapamil and diltiazem, may exert negative inotropic effects and destabilize previously asymptomatic patients. Accordingly, their use should be discouraged in patients with HFrEF.

■ ANTI-INFLAMMATORY THERAPY

Targeting inflammatory cytokines such as tumor necrosis factor α (TNF- α) for the management of HF by using anticytokine agents such as infliximab and etanercept has been unsuccessful and associated with worsening HF. Use of intravenous immunoglobulin therapy in nonischemic etiology of HF has not been shown to result in beneficial outcomes. Nonspecific immunomodulation has been tested in the Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy (ACCLAIM-HF) trial where *ex vivo* exposure of a blood sample from systolic HF patients to controlled oxidative stress was hypothesized to initiate apoptosis of leukocytes soon after intramuscular gluteal injection of the treated sample. The physiologic response to apoptotic cells results in a reduction in inflammatory cytokine production and upregulation of anti-inflammatory cytokines. This promising hypothesis was not proven, although certain subgroups (those with no history of previous myocardial infarction and those with mild HF) showed signals in favor of immunomodulation. Most recently, in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), treatment of post-myocardial infarction patients with elevated high-sensitivity C-reactive protein using a monoclonal antibody targeted at interleukin 1 β was associated with a dose-dependent reduction in hospitalization for HF and HF-associated mortality in post hoc analyses. Whether this approach might have relevance for patients with established HF remains unclear.

■ HMG-CoA REDUCTASE INHIBITORS (STATINS)

Potent lipid-altering and pleiotropic effects of statins reduce major cardiovascular events and improve survival in non-HF populations. Once HF is well established, this therapy may not be as beneficial and theoretically could even be detrimental by depleting ubiquinone in the electron transport chain. Two trials, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF), have tested low-dose rosuvastatin in patients with HFrEF and demonstrated no improvement in aggregate clinical outcomes. If statins are required to treat progressive atherosclerotic vascular disease or significant dyslipidemia in the background setting of HF, then they should be employed. However, no clear rationale appears to exist for routine use of statin therapy in nonischemic HF.

■ ANTICOAGULATION AND ANTIPLATELET THERAPY

HFrEF is accompanied by a hypercoagulable state and therefore a high risk of thromboembolic events, including stroke, pulmonary embolism, and peripheral arterial embolism. Although the value of long-term oral anticoagulation is established in certain groups, including patients with atrial fibrillation, the data are insufficient to support the use of warfarin in patients in normal sinus rhythm without a history of thromboembolic events or echocardiographic evidence of left ventricular thrombus. In the large Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, full-dose aspirin or international normalized ratio-controlled warfarin was tested with follow-up for 6 years. Among patients with reduced LVEF in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. A recent trial of the direct oral anticoagulant rivaroxaban at low dose (2.5 mg daily) for patients with ischemic heart disease, HFrEF, and sinus rhythm also indicated no reduction in stroke or ischemic events compared with placebo. Aspirin blunts ACEI-mediated prostaglandin synthesis, but the clinical importance of this finding remains unclear. Current guidelines support the use of aspirin in patients with ischemic cardiomyopathy who do not have a contraindication, although the risk-benefit balance in older patients at higher risk for bleeding complications may be less favorable.

■ FISH OIL

Treatment with long-chain omega-3 polyunsaturated fatty acids (ω -3 PUFAs) has been shown to be associated with modestly improved

clinical outcomes in patients with HFrEF. This observation from the GISSI-HF trial was extended to measurements of ω -3 PUFAs in plasma phospholipids at baseline and after 3 months. Three-month treatment with ω -3 PUFAs enriched circulating eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Low EPA levels are inversely related to total mortality in patients with HFrEF.

■ MICRONUTRIENTS

A growing body of evidence suggests an association between HF and micronutrient status. Reversible HF has been described because of severe thiamine and selenium deficiency. Thiamine deficiency has received attention in HF because malnutrition and diuretics are prime risk factors for thiamine loss. Small exploratory randomized studies have suggested a benefit of supplementation with thiamine in HFrEF with evidence of improved cardiac function. This finding is restricted to chronic HF states and does not appear to be beneficial in the ADHF phenotype. Due to the exploratory nature of the evidence, no recommendations for routine supplementation or testing for thiamine deficiency can be made.

■ ENHANCED EXTERNAL COUNTERPULSATION

Peripheral lower extremity therapy using graded external pneumatic compression at high pressure is administered in 1-h sessions for 35 treatments (7 weeks) and has been proposed to reduce angina symptoms and extend time to exercise-induced ischemia in patients with coronary artery disease. The Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) study assessed the benefits of enhanced external counterpulsation in the treatment of patients with mild-to-moderate HF. This randomized trial improved exercise tolerance, QOL, and NYHA functional classification but without an accompanying increase in peak oxygen consumption. A placebo effect due to the nature of the intervention simply cannot be excluded.

■ EXERCISE

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study investigated short-term (3-month) and long-term (12-month) effects of a supervised exercise training program in patients with moderate HFrEF. Exercise was safe, improved patients' sense of well-being, and correlated with a trend toward mortality reduction. Maximal changes in 6-min walk distance were evident at 3 months with significant improvements in cardiopulmonary exercise time and peak oxygen consumption persisting at 12 months. Therefore, exercise training is recommended as an adjunctive treatment in patients with HF.

■ MANAGEMENT OF SELECTED COMORBIDITY

Sleep-disordered breathing is common in HF and particularly in HFrEF. A range of presentations exemplified by obstructive sleep apnea, central sleep apnea, and its extreme form of Cheyne-Stokes breathing are noted. Frequent periods of hypoxia and repeated micro- and macro-arousals trigger adrenergic surges, which can worsen hypertension and impair systolic and diastolic function. A high index of suspicion is required, especially in patients with difficult-to-control hypertension or with predominant symptoms of fatigue despite reverse remodeling in response to optimal medical therapy. Worsening of right heart function with improvement of left ventricular function noted on medical therapy should immediately trigger a search for underlying sleep-disordered breathing or pulmonary complications such as occult embolism or pulmonary hypertension. Treatment with nocturnal positive airway pressure improves oxygenation, LVEF, and 6-min walk distance. However, no conclusive data exist to support this therapy as a disease-modifying approach with reduction in mortality. A recent trial using adaptive servo-ventilation triggered by a minute ventilation sensor in patients who had HFrEF and predominantly central sleep apnea increased all-cause and cardiovascular mortality, so this approach should be avoided; however, modification of this approach using lower background pressures and an alternative trigger based on peak airflow appeared to be safe in patients with sleep apnea and HFrEF enrolled in the ADVENT-HF trial, although there was

no discernible benefit with regard to clinical outcomes. Whether this modified approach to adaptive servo-ventilation will be appropriate for management of selected patients with HFrEF and central sleep apnea requires further study.

Anemia is common in HF patients, reduces functional status and QOL, and is associated with increased proclivity for hospital admissions and mortality. Anemia in HF is more common in the elderly, in those with advanced stages of HFrEF, in the presence of renal insufficiency, and in women and African Americans. The mechanisms include iron deficiency, dysregulation of iron metabolism, and occult gastrointestinal bleeding. Intravenous iron using either iron sucrose or carboxymaltose (Ferric Carboxymaltose Assessment in Patients with Iron Deficiency and Chronic Heart Failure [FAIR-HF] trial) has been shown to correct anemia and improve functional capacity. Another trial, CONFIRM-HF, enrolled similar patients with iron deficiency (ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation <20%) and demonstrated that use of ferric carboxymaltose in a simplified high-dose schedule resulted in improvement in functional capacity, symptoms, and QOL. These symptomatic benefits of iron repletion, however, do not appear to translate clearly to benefits on longer term clinical outcomes. In the AFFIRM-AHF trial of patients with HF, LVEF <50%, and iron deficiency, randomization to ferric carboxymaltose compared with placebo was associated with a lower rate of cardiovascular death and total HF hospitalizations that narrowly missed the margin for statistical significance. Similar results were seen in the IRONMAN trial of another iron polysaccharide, ferric derisomaltose. The results of both of these trials may have been confounded by the coronavirus disease 2019 (COVID-19) pandemic, and pooled data suggested a possible favorable effect on HF hospitalizations. However, the HEART-FID trial, which randomized 3065 ambulatory HF patients with LVEF ≤40% and iron deficiency to treatment with ferric carboxymaltose or placebo, showed no benefit with regard to the primary hierarchical composite of death, hospitalizations for HF, or 6-minute walk distance. Accordingly, it seems that benefits of iron repletion in this population are likely confined to reduction in symptoms, and perhaps HF hospitalizations, particularly among those with iron deficiency. Oral iron supplementation does not appear to be effective in treating iron deficiency in HF. Erythropoiesis-regulating agents such as erythropoietin analogues have been studied with disappointing results. The Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial demonstrated that treatment with darbepoetin alfa did not improve outcomes in patients with systolic HF but increased the risk of thromboembolism-related adverse events.

Depression is common in HFrEF, with a reported prevalence of one in five patients, and is associated with a poor QOL, limited functional status, and increased risk of morbidity and mortality in this population. However, the largest randomized study of depression in HFrEF, the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) trial, showed that although sertraline was safe, it did not provide greater reduction in depression or improve cardiovascular status among patients with HF and depression compared with nurse-driven multidisciplinary management.

Atrial arrhythmias, especially atrial fibrillation, are common and serve as a harbinger of worse prognosis in patients with HF. When rate control is inadequate or symptoms persist, pursuing a rhythm control strategy is reasonable. Rhythm control may be achieved via pharmacotherapy or by percutaneous or surgical techniques, and referral to practitioners or centers experienced in these modalities is recommended. Antiarrhythmic drug therapy should be restricted to amiodarone and dofetilide, both of which have been shown to be safe and effective but do not alter the natural history of the underlying disease. The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) studied the effects of the novel antiarrhythmic agent dronedarone and found an increased mortality due to worsening HF. Given the potential adverse effects and limited efficacy of pharmacologic strategies for maintenance of sinus rhythm, catheter ablation has been explored as an alternative. In the CASTLE-AF trial, among

363 patients with HF, LVEF ≤35%, and paroxysmal or persistent atrial fibrillation randomized to treatment with catheter ablation or medical therapy, those assigned to catheter ablation experienced a significantly lower rate of death or hospitalization. These results are supported by similar outcomes in the CASTLE-HTX trial, which sought to include patients with advanced HF; however, this aspect is disputed. These data argue for consideration of restoration of sinus rhythm with catheter ablation as a preferred strategy to antiarrhythmic drugs in patients with HF and reduced EF.

Diabetes mellitus is a frequent comorbidity in HF. Prior studies using thiazolidinediones (activators of peroxisome proliferator-activated receptors) have been associated with worsening HF. GLP-1 agonists such as liraglutide have also been tested and do not lead to worsening in HF but require more study. The role of SGLT-2 inhibitors in HF has been previously discussed, and they represent an important disease-modifying therapy in diabetic patients with HF.

■ NEUROMODULATION USING DEVICE THERAPY

Autonomic dysfunction is common in HF, and attempts at using devices to modulate the sympathetic and parasympathetic systems have been undertaken. Broadly, devices that achieve vagal nerve stimulation, baroreflex activation, renal sympathetic denervation, spinal cord stimulation, or left cardiac sympathetic denervation have been employed. While small preclinical and clinical studies have demonstrated benefits, large, randomized trials, when conducted, have failed. The INOVATE-HF study tested vagal nerve stimulation versus optimal medical therapy among individuals with stable HF. Vagus nerve stimulation did not reduce the rate of death or hospitalization for HF. However, functional capacity and QOL were favorably affected by vagus nerve stimulation. The ANTHEM-HFrEF trial, which enrolled only half its intended population, did not show a signal for benefit of vagal nerve stimulation.

■ CARDIAC CONTRACTILITY MODULATION

Cardiac contractility modulation (CCM) is a device-based therapy for HF that involves nonexcitatory electrical stimulation to the right ventricular septal wall during the absolute myocardial refractory period to augment the strength of subsequent myocardial contraction. A series of small, randomized, prospective clinical trials, as well as several real-world observational registries, have suggested that application of CCM to selected patients with HF may improve symptoms, functional capacity, and QOL, although no effect on hard clinical outcomes such as HF hospitalization or mortality has been established. The predominant benefits of CCM appear to accrue to those with symptomatic HFrEF (EF 25–45%) and narrow QRS duration (for whom cardiac resynchronization therapy is not an option), and the approach can be combined with an implantable defibrillator. The device is not currently endorsed for routine use by clinical treatment guidelines in the United States or Europe and is deemed to require more evidence prior to widespread adoption.

CARDIAC RESYNCHRONIZATION THERAPY

Nonsynchronous contraction between the walls of the left ventricle (intraventricular) or between the ventricular chambers (interventricular) impairs systolic function, decreases mechanical efficiency of contraction, and adversely affects ventricular filling. Mechanical dyssynchrony results in an increase in wall stress and worsens functional mitral regurgitation. The single most important association of extent of dyssynchrony is a widened QRS interval on the surface electrocardiogram, particularly in the presence of a left bundle branch block pattern. With placement of a pacing lead via the coronary sinus to the lateral wall of the ventricle, cardiac resynchronization therapy (CRT) enables a more synchronous ventricular contraction by aligning the timing of activation of the opposing walls. Early studies showed improved exercise capacity, reduction in symptoms, and evidence of reverse remodeling. The Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial was the first study to demonstrate a reduction in all-cause mortality with CRT placement in patients with HFrEF on optimal therapy with continued moderate-to-severe residual symptoms of

NYHA class III or IV HF. More recent clinical trials have demonstrated disease-modifying properties of CRT in even minimally symptomatic patients with HFrEF, including the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), both of which sought to use CRT in combination with an implantable defibrillator. Most benefit in mildly symptomatic HFrEF patients accrues from applying this therapy in those with a QRS width of >149 ms and a left bundle branch block pattern. Attempts to further optimize risk stratification and expand indications for CRT using modalities other than electrocardiography have proven disappointing. Echocardiographically derived measures of dyssynchrony vary tremendously, and narrow QRS dyssynchrony has not proven to be a good target for treatment. Uncertainty surrounds the benefits of CRT in those with ADHF, a predominant right bundle branch block pattern, atrial fibrillation, and evidence of scar in the lateral wall, which is the precise location where the CRT lead is positioned. His-Purkinje conduction system or left bundle branch area pacing are evolving alternatives to biventricular pacing; however, the evidence supporting their benefits over conventional CRT remains less certain.

SUDDEN CARDIAC DEATH PREVENTION IN HEART FAILURE

Sudden cardiac death (SCD) due to ventricular arrhythmias is the mode of death in approximately half of patients with HF and is particularly proportionally prevalent in HFrEF patients with early stages of the disease. Patients who survive an episode of SCD are at very high risk and qualify for placement of an implantable cardioverter-defibrillator (ICD). Although primary prevention is challenging, the degree of residual left ventricular dysfunction despite optimal medical therapy ($\leq 35\%$) to allow for adequate remodeling and the underlying etiology (post-myocardial infarction or ischemic cardiomyopathy) are the two single most important risk markers for stratification of need and benefit. Currently, patients with NYHA class II or III symptoms of HF and an LVEF $< 35\%$, irrespective of etiology of HF, are appropriate candidates for ICD prophylactic therapy. In patients with a myocardial infarction and optimal medical therapy with residual LVEF $\leq 30\%$ (even when asymptomatic), placement of an ICD is appropriate. A recent Danish trial suggested that prophylactic ICD implantation in patients with symptomatic systolic HF not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. In this trial, benefits were noted in those aged < 60 years. In patients with a terminal illness and a predicted life span of < 6 months or in those with NYHA class IV symptoms who are refractory to medications and who are not candidates for transplant, the risks of multiple ICD shocks must be carefully weighed against the survival benefits. If a patient meets the QRS criteria for CRT, combined CRT with ICD is often employed (Table 265-3).

SURGICAL THERAPY IN HEART FAILURE

Coronary artery bypass grafting (CABG) is considered in patients with ischemic cardiomyopathy with multivessel coronary artery disease. The recognition that hibernating myocardium, defined as myocardial tissue with abnormal function but maintained cellular function, could recover after revascularization led to the notion that revascularization with CABG would be useful in those with living myocardium. Revascularization is most robustly supported in individuals with ongoing angina and left ventricular failure. Revascularizing those with left ventricular failure in the absence of angina remains controversial. The Surgical Treatment for Ischemic Heart Failure (STICH) trial in patients with an EF of $\leq 35\%$ and coronary artery disease amenable to CABG demonstrated no significant initial benefit compared to medical therapy. However, patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes over 10 years than among those who received medical therapy alone. An ancillary study of this trial also determined that the detection of hibernation (viability) before revascularization did not materially influence the efficacy of this

TABLE 265-3 Principles of ICD Implantation for Primary Prevention of Sudden Death

PRINCIPLE	COMMENT
Arrhythmia–sudden death mismatch	Sudden death in heart failure patients is generally due to progressive LVD, not a focal arrhythmia substrate (except in patients with post-MI HF with scar)
Diminishing returns with advanced disease	Intervention at early stages of HF most successful since sudden death incidence diminishes as cause of death with increasing severity of HF
Timing of benefits	LVEF should be evaluated on optimal medical therapy or after revascularization before ICD therapy is employed; no benefit to ICD implant within 40 days of an MI (unless for secondary prevention)
Estimation of benefits and prognosis	Patients and clinicians often overestimate benefits of ICDs; an ICD discharge is not equivalent to an episode of sudden death (some ventricular arrhythmias terminate spontaneously); appropriate ICD discharges are associated with a worse near-term prognosis; recent trials with uncertain benefit in nonischemic cardiomyopathy (especially in those > 68 years old)

Abbreviations: HF, heart failure; ICD, implantable cardioverter-defibrillator; LVD, left ventricular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

approach, nor did it help to define a population unlikely to benefit if hibernation was not detected. Notably, a strategy of percutaneous coronary revascularization in patients with ischemic left ventricular dysfunction in the REVIVED-BCIS2 study did not show clinical benefit.

Surgical ventricular restoration (SVR), a technique characterized by infarct exclusion to remodel the left ventricle by reshaping it surgically in patients with ischemic cardiomyopathy and dominant anterior left ventricular dysfunction, has been proposed. However, in a 1000-patient trial in patients with HFrEF who underwent CABG alone or CABG plus SVR, the addition of SVR to CABG had no disease-modifying effect. However, left ventricular aneurysm surgery is still advocated in those with refractory HF, ventricular arrhythmias, or thromboembolism arising from an akinetic aneurysmal segment of the ventricle. Other remodeling procedures, such as use of an external mesh-like net attached around the heart to limit further enlargement, have not been shown to provide hard clinical benefits, although favorable cardiac remodeling was noted.

Functional (or secondary) mitral regurgitation (MR) occurs with varying degrees in patients with HFrEF and dilated ventricles, and its severity is correlated inversely with prognosis. Annular dilatation and leaflet noncoaptation related to distorted papillary muscle geometry in the context of ventricular remodeling is typically responsible, although in patients with ischemic heart disease and prior myocardial infarction, leaflet tethering and displacement may contribute. The primary approach to management of functional MR is optimization of guideline-directed medical therapy, followed by CRT in eligible patients, but relief may be incomplete for many patients with advanced HF. In these patients with HF and severe left ventricular dysfunction who are not candidates for surgical coronary revascularization, surgical mitral valve repair (MVR) to remedy functional MR carries significant risk and remains controversial. The development of percutaneous approaches to edge-to-edge MVR has provided a less invasive approach that enables reduction in functional MR at lower risk than conventional surgery. Recently, two large, randomized trials of transcatheter MVR using this approach have been conducted in patients with symptomatic HFrEF and moderate-severe functional MR. In the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) study, patients allocated to MVR versus standard HF therapy experienced a marked reduction in both HF hospitalizations and mortality at 2 years, supporting the efficacy of this approach. In the second trial, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR), which employed a similar design, the rates of

death or HF hospitalization did not differ between the percutaneous MVR and medical therapy groups. The precise reason for discrepant results between these studies remains unclear but may be related to differences in background utilization of guideline-directed medical therapy, procedural success rates, and patient selection (particularly whether the severity of MR is proportionate or disproportionate to the degree of left ventricular cavity dilation). Because mortality rates at 2 years remain high even with percutaneous MVR, patients with advanced symptoms of HF in whom MR severity is driven principally by end-stage left ventricular remodeling should also be considered for advanced therapies such as mechanical circulatory support if symptoms remain refractory to medical therapy.

CELLULAR AND GENE-BASED THERAPY

The cardiomyocyte possesses regenerative capacity, and such renewal is accelerated under conditions of stress and injury, such as an ischemic event or HF. Investigations that use either bone marrow-derived precursor cells or autologous cardiac-derived cells have gained traction but have not generally improved clinical outcomes in a convincing manner. More promising, however, are cardiac-derived stem cells. Two preliminary pilot trials delivering cells via an intracoronary approach have been reported. In one, autologous c-kit-positive cells isolated from the atria obtained from patients undergoing CABG were cultured and reinfused. In another, cardiosphere-derived cells grown from endomyocardial biopsy specimens were used. These small trials demonstrated improvements in left ventricular function but require far more work to usher in a clinical therapeutic success. Efforts to utilize mesenchymal stem cells to facilitate left ventricular recovery and weaning from mechanical circulatory support in patients with left ventricular assist devices have also been disappointing. The appropriate route of administration, the quantity of cells to achieve a minimal therapeutic threshold, the constitution of these cells (single source or mixed), the mechanism by which benefit accrues, and short- and long-term safety remain to be elucidated.

Targeting molecular aberrations using gene transfer therapy, mostly with an adenoviral vector, has been tested in HFrEF. A cellular target includes calcium cycling proteins such as inhibitors of phospholamban such as SERCA2a, which is deficient in patients with HFrEF. Primarily responsible for reincorporating calcium into the sarcoplasmic reticulum during diastole, this target was tested in the CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure) trial. This study used coronary arterial infusion of adeno-associated virus type 1 carrying the gene for SERCA2a and initially demonstrated that natriuretic peptides were decreased, reverse remodeling was noted, and symptomatic improvements were forthcoming. However, a confirmatory trial failed to meet its primary efficacy endpoint. The DREAM-HF trial was a randomized, double-blind, multicenter study of a single transcatheter administration of mesenchymal precursor cells in patients in HFrEF. The primary and secondary endpoints of the trial were negative.

More advanced therapies for late-stage HF such as left ventricular assist devices and cardiac transplantation are covered in detail in Chap. 271.

DISEASE MANAGEMENT AND SUPPORTIVE CARE

Despite stellar outcomes with medical therapy, admission rates following HF hospitalization remain high, with nearly half of all patients readmitted to hospital within 6 months of discharge. Recurrent HF and related cardiovascular conditions account for only half of readmissions in patients with HF, whereas other comorbidity-related conditions account for the rest. The key to achieving enhanced outcomes must begin with the attention to transitional care at the index hospitalization with facilitated discharge through comprehensive discharge planning, patient and caregiver education, appropriate use of visiting nurses, and planned follow-up. Early postdischarge follow-up, whether by telephone or clinic-based, may be critical to ensuring

stability because most HF-related readmissions tend to occur within the first 2 weeks after discharge. The results of the recent STRONG-HF trial suggest that a strategy of intensive titration of medical therapy to guideline-recommended targets within 2 weeks of hospital discharge and frequent ambulatory follow-up through 2 months is associated with a substantial reduction in all-cause mortality and HF readmission at 180 days, underscoring the importance of timely application of targeted pharmacologic therapy and intensive clinical surveillance in the early postdischarge interval.

Although routinely advocated, intensive surveillance of weight and vital signs with use of telemonitoring has not decreased hospitalizations. Serial measurement of intrathoracic impedance has been utilized to identify early signals of worsening congestion to guide preemptive management to obviate the need for hospitalization. However, when systematically studied in randomized trials, this approach has not been proven to improve outcomes in comparison with routine HF care and may even enhance the rate of hospitalization due to the high frequency of impedance threshold crossings and device alerts. Implantable hemodynamic monitoring systems that directly measure pulmonary artery pressure tend to provide signals for early decompensation, and in patients with HF and moderately advanced symptoms across the full spectrum of EF, such systems have been shown to provide information that can allow implementation of therapy to avoid hospitalizations by as much as 39% (in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients [CHAMPION] trial). More recently, in the larger Hemodynamic Guided Management of Heart Failure (GUIDE-HF) Trial, hemodynamic-guided management with the same sensor did not result in a lower rate of composite mortality and total HF events in the primary analysis, the results of which were confounded by the impact of the COVID-19 pandemic on overall hospitalization rates. In a prespecified analysis of patients enrolled prior to the pandemic onset, there was a statistically significant reduction in the composite endpoint driven by lower rates of HF hospitalization in those assigned to the hemodynamic-guided therapy arm. Benefits were consistent across patients with prior HF hospitalization within 12 months and in those with elevated natriuretic peptide levels but no recent hospitalization. These data in aggregate suggest that hemodynamic-guided management is a useful adjunct to routine clinical care in selected high-risk patients with chronic HF across the spectrum of EF. Alternate approaches to longitudinal HF monitoring that leverage multiparameter signals derived from implantable cardiac rhythm devices such as pacemakers and defibrillators to provide a global index of congestion are also being explored as adjuncts to longitudinal HF management.

Once HF becomes advanced, regularly scheduled review of the disease course and options with the patient and family is recommended, including discussions surrounding end-of-life preferences when patients are comfortable in an outpatient setting. As the disease state advances further, integrating care with social workers, pharmacists, and community-based nursing may be critical in improving patient satisfaction with the therapy, enhancing QOL, and avoiding HF hospitalizations. Equally important is attention to seasonal influenza vaccinations and periodic pneumococcal vaccines that may obviate non-HF hospitalizations in these ill patients. When nearing end of life, facilitating a shift in priorities to outpatient and hospice palliation is key, as are discussions around advanced therapeutics and continued use of ICD prophylaxis, which may worsen QOL and prolong death. Small, randomized trials have suggested that systematic integration of palliative care considerations in high-risk HF patients by a specialized team has been demonstrated to improve QOL, anxiety, depression, and spiritual well-being and to facilitate goal-concordant care.

GLOBAL CONSIDERATIONS

Substantial differences exist in the practice of HF therapeutics and outcomes by geographic location. The penetrance of CRT and ICD is higher in the United States than in Europe. Conversely, therapy unavailable in the United States, such as levosimendan, is designated

as useful in Europe, although the usefulness is disputable. Variation in the benefits of beta blockers based on world region remains an area of controversy. In oral pharmacologic therapy trials of HF_{rEF}, patients from southwest Europe have a lower incidence of ischemic cardiomyopathy and those in North America tend to have more diabetes and prior coronary revascularization. There is also regional variation in medication use even after accounting for indication. In trials of HF, disparate effects are noted across populations. As a recent example, in TOPCAT, the drug spironolactone was effective when used in the U.S. population, whereas patients recruited from Russia and contiguous territories showed no difference. Whether this represents population differences or trial conduct disparity remains a serious question. ADHF patients in Eastern Europe tend to be younger, with higher EFs and lower natriuretic peptide levels. Patients from South America tend to have the lowest rates of comorbidities, revascularization, and device use. In contrast, patients from North America have the highest comorbidity burden with high revascularization and device use rates. Given geographic differences in baseline characteristics and clinical outcomes, the generalizability of therapeutic outcomes in patients in the United States and Western Europe may require verification.

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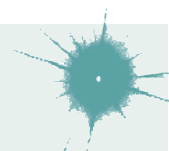
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266

Classification of Cardiomyopathy

Lynne Warner Stevenson, Neal K. Lakdawala,
Joseph Loscalzo



The term *cardiomyopathy* describes primary disease of the heart muscle itself, originally excluding myocardial dysfunction resulting from other cardiovascular disease. Common usage, however, often includes diagnoses of ischemic cardiomyopathy, valvular cardiomyopathy, and hypertensive cardiomyopathy. The traditional morphologic classification defines the three major phenotypes of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and restrictive cardiomyopathy (RCM) ([Table 266-1](#)).

Left ventricular wall thickness is increased (≥ 13 –15 mm depending on context) and ejection fraction is normal or high with HCM. DCM is defined when the left ventricular ejection fraction (LVEF) is ≤ 0.50 , but most clinical presentations are with LVEF ≤ 0.40 . RCMs typically present with mildly decreased ejection fraction and variably increased wall thickness and are often defined less by morphology than by evidence of abnormal diastolic physiology on echocardiography or invasive hemodynamic measurement.

Although these phenotypes are helpful to guide initial evaluation of clinical disease, the phenotypes increasingly overlap over time as there is increasing recognition that DCMs can respond to recommended therapies with “reverse remodeling” to higher ejection fraction and smaller ventricles, while HCM evolves in ~5% of patients to a reduced ejection fraction (HCM-rEF) with more restrictive physiology. A fourth evolving phenotype with predominantly genetic causes is arrhythmogenic right ventricular cardiomyopathy (ARVC), originally termed *arrhythmogenic right ventricular dysplasia*, characterized by life-threatening arrhythmias and abnormal right ventricular structure and function, with variable expression in the left ventricle. As new phenotype-genotype connections are revealed, the terminology continues to evolve, as arrhythmogenic right ventricular dysplasia may also be termed ACM-RV (arrhythmogenic cardiomyopathy–right ventricle predominant), in line with ACM-LV, in which the arrhythmias and structural changes are predominantly in the left ventricle. If the ACM terminology is expanded to include acquired disease, the granulomatous disease of sarcoidosis and the protozoal myocarditis of Chagas’ disease can both cause phenotypes with cardiomyopathy and ventricular arrhythmias that qualify as ACM-RV and ACM-LV.

Reliance upon phenotypic presentation is diminishing as more is learned about the underlying causes of cardiomyopathy. The catalog is rapidly growing of pathogenic genetic variants that can lead to heritable cardiomyopathies, which new imaging techniques can now sometimes identify prior to clinical disease. Expanding knowledge of immune response pathways reveals how some aspects of myocarditis may also be inherited and how they contribute to infectious and noninfectious inflammation that can cause clinical myocarditis and cardiomyopathy. Diagnosis and outcomes of clinical cardiomyopathies are further complicated by the frequent two-hit models where the clinical expression of a genetic predisposition to cardiomyopathy may

Mid-range LVEF (0.40–0.50)

TABLE 266-1 Classification of Cardiomyopathies

CARDIOMYOPATHY (CM) PHENOTYPE	DIAGNOSTIC CRITERIA	OTHER MORPHOLOGY	COMMON CHALLENGES IN DIAGNOSIS
Hypertrophic cardiomyopathy (HCM) <i>Mid-range LVEF includes rare transition to HCM with LV systolic dysfunction (LVEF <0.50)</i>	Septal thickness in men ≥ 15 mm, ≥ 13 mm in women. 13–14 mm may be diagnostic in relatives of proband with known HCM or with positive genetic test. LVEF $\geq$ normal, usually >0.60 LV chamber volume $\leq$ normal.	Patterns of LV hypertrophy (LVH) in HCM: • Asymmetric septal hypertrophy • Inverse (sigmoid pattern) septal hypertrophy • Concentric LVH • Apical hypertrophy	Distinction from athlete's heart and severe chronic hypertension The storage diseases of <i>GLA</i> (Anderson-Fabry), <i>PRKAG2</i> , and <i>LAMP2</i> (Danon's), which can mimic HCM morphology Exclude aortic stenosis In older patients, exclude amyloidosis, which can also cause asymmetric septal thickening
Restrictive cardiomyopathy (RCM) Least common cardiomyopathy (CM) phenotype	Functional diagnosis based on moderate-severe diastolic dysfunction and/or elevated cardiac filling pressures. Wall thickness often increased but can appear normal. LVEF usually mildly reduced, occasionally normal.	Usually marked atrial enlargement Although both ventricles affected, clinical right heart failure often dominates. Marked wall thickness suggests: • Amyloidosis • Inherited storage diseases • Inborn metabolic diseases	Common etiologies of radiation, scleroderma-type connective tissue diseases, doxorubicin and other medications Some sarcomeric variants and storage diseases can appear with RCM as well as HCM phenotypes Although traditionally listed as restrictive, sarcoidosis more often has morphology of regional wall motion abnormalities, DCM phenotype, or right ventricular (RV) involvement with systolic dysfunction
<i>Mid-range LVEF is often a transition in DCM, either deterioration from early DCM or improvement into DCM remission</i> LV dilated cardiomyopathy (DCM)	• Early: LVEF ≤ 0.50 and/or LVEDV $>112\%$ normal for age/sex or LVEDD $>95\%$ predicted sex/height • LVEF ≤ 0.40 : threshold for traditionally recommended therapies for heart failure with low LVEF • Persistent LVEF ≤ 0.30 – 0.35 : threshold for primary prevention ICD	Can involve LV alone or with RV involvement either from primary cause or from secondary RV failure due to chronically elevated pulmonary artery pressures	Structural heart disease such as coronary artery disease or infarction from other cause, primary valve disease
<i>Arrhythmogenic CM Dominant in LV (ACM-LV)</i> Usually DCM, occasionally RCM	Morphologic criteria generally those for DCM. <i>Ventricular tachyarrhythmias dominate without or before severely reduced LVEF and heart failure.</i> Primary prevention ICD considered even when LVEF >0.35 .	Suggestive but not necessarily conclusive differences in patterns of late gadolinium enhancement between different variants Occasional ACM-LV with RCM phenotype	For frequent PVCs or NSVT, may be difficult to distinguish PVC-related CM from genetic CM causing both the arrhythmias and the CM
<i>Arrhythmogenic CM Dominant in RV (ACM-RV; also termed ARVC)</i> <i>Biventricular arrhythmogenic CM</i>	Modified task force criteria from 2010 include combinations of major and minor criteria <i>Ventricular arrhythmias and evidence of both ACM-RV and ACM-LV</i>	Abnormal RV function or structure <i>Biventricular ACM often diagnosed from LGE in ventricle with less involvement</i>	Cardiac sarcoidosis can cause predominantly RV involvement with ventricular arrhythmias, RV wall motion abnormalities, aneurysms, and dilation
Trait of LV noncompaction (LVNC) Implications determined by CM phenotype and genotype	Often assessed by maximum ratio of noncompacted/compacted LV myocardium >2.3 and other criteria	Can occur with HCM, DCM, some dystrophies, and other syndromic presentations	Can occur in normal hearts, pregnancy Increased prevalence in athletic hearts

Abbreviations: ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction.

be triggered by acquired conditions such as infections, toxic exposures, pregnancy, or tachycardia.

CLINICAL PRESENTATION AND EVALUATION OF CARDIOMYOPATHY

Early symptoms of cardiomyopathy often reflect exertional intolerance with breathlessness or fatigue. Arrhythmias are often presenting events of unrecognized cardiomyopathy, which can also present with embolic events related to atrial fibrillation or apical ventricular thrombi. Cardiomyopathy may often present first with the syndrome of congestion, with fluid retention and elevated left heart filling pressures causing shortness of breath with minimal activity or even at rest, particularly with orthopnea. It may be accompanied by elevated right-sided filling pressures causing edema and often abdominal symptoms. The non-specific historical term *congestive heart failure* describes the syndrome

of congestion, which is common to diverse cardiac diagnoses such as congenital heart disease, primary pulmonary hypertension, and structural valve disease. “Congestive heart failure” should not be considered a diagnosis or an etiology of cardiomyopathy but a nonspecific syndrome requiring thorough evaluation of possible etiology/ies. Initial evaluation of possible cardiomyopathy begins with a detailed clinical history and examination seeking clues to cardiac, genetic, and systemic causes of heart disease, which help to guide subsequent evaluation (Table 266-2).

Echocardiography remains the initial imaging modality to define morphology and function, with increasing use of magnetic resonance imaging to provide further information on myocardial tissue characterization, patterns of fibrosis indicated by late gadolinium enhancement, and T1 and T2 mapping for evidence of focal and diffuse inflammation.

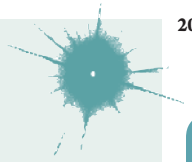


TABLE 266-2 Initial Evaluation of Cardiomyopathy

Clinical Evaluation

Thorough history and physical examination to identify cardiac and noncardiac disorders

Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders, tachyarrhythmias, and sudden death

History of alcohol, illicit drugs, chemotherapy or radiation therapy

Assessment of changing ability to perform routine and desired activities

Assessment of jugular venous pressure, edema, orthostatic blood pressure, adequacy of perfusion

Laboratory Evaluation

Electrocardiogram

Chest radiograph

Two-dimensional and Doppler echocardiogram

Magnetic resonance imaging for evidence of myocardial inflammation and fibrosis

Chemistry:

Serum sodium, potassium, calcium, magnesium

Fasting glucose (glycohemoglobin in diabetes mellitus)

Creatinine, blood urea nitrogen

Albumin, total protein, liver function tests

Lipid profile

Thyroid-stimulating hormone

Serum iron, transferrin saturation

Urinalysis

Creatine kinase isoforms

Cardiac troponin level

Hematology:

Hemoglobin/hematocrit

White blood cell count with differential

Total eosinophil count if abnormal % on differential

Erythrocyte sedimentation rate

Evaluation When Specific Diagnoses Are Suspected

Respiratory pathogen panel during acute respiratory syndromes

Diagnosis of other specific infections such as:

Human immunodeficiency virus

Chagas' disease (*Trypanosoma cruzi*)

Lyme disease (*Borrelia burgdorferi*) and other tick-borne diseases

Toxoplasmosis

Trichinosis

Genetic counseling and testing with multigene cardiomyopathy panel

Serologies for active rheumatologic disease

Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications

Catheterization with coronary angiography in patients who have evidence of ischemia/infarction and are candidates for intervention

267 Genetic Cardiomyopathies

Neal K. Lakdawala, Lynne Warner
Stevenson, Joseph Loscalzo

Each of the traditional morphologic forms of cardiomyopathy, hypertrophic, dilated, and restrictive, can be caused or modified by underlying genetic factors (Table 267-1). Estimates for the prevalence of a genetic etiology for cardiomyopathy continue to rise, with increasing availability of genetic testing and attention to the family history. Well-recognized in hypertrophic cardiomyopathy, heritability is also present in at least 30% of dilated cardiomyopathy (DCM) without other clear etiology. Careful family history should elicit information about not only known cardiomyopathy and heart failure, but also family members who have had sudden death, often incorrectly attributed to a "heart attack," who have had atrial fibrillation or pacemaker implantation by middle age, or who have muscular dystrophy.

Most familial cardiomyopathies are inherited in an autosomal dominant pattern, with occasional autosomal recessive, matrilineal (mitochondrial), and X-linked inheritance (Table 267-1). Missense variants with amino acid substitutions and truncating variants are the most common genetic abnormalities in cardiomyopathy. Expressed mutant proteins may interfere with function of the normal allele through a dominant negative mechanism. Variants introducing a premature stop codon (nonsense) or shift in the reading frame (frameshift) may create a truncated or unstable protein, the lack of which causes cardiomyopathy (haploinsufficiency). In some forms of genetic DCM, both haploinsufficiency and the dominant negative effect of a truncated allele may contribute to pathophysiology. Deletions or duplications of an entire exon or gene are uncommon causes of cardiomyopathy, except for the dystrophinopathies.

Many different genes have been implicated in human cardiomyopathy (locus heterogeneity), and many pathogenic or likely pathogenic variants (i.e., variants) within those genes have been associated with disease (allelic heterogeneity). Although most identified variants are "private" to individual families, several specific variants are found repeatedly, either due to a founder effect or recurrent variants at a common residue. While most patients with genetic cardiomyopathy have a single rare, "high effect," disease allele, there is a growing appreciation for the effect of multiple less rare "intermediate effect" alleles on penetrance and expression. While the additive effects of multiple common alleles/variants captured as a polygenic risk score have shown greatest utility in common diseases such as atherosclerosis, they may also provide insight into the subset of patients with primary cardiomyopathy without an identifiable "high effect" allele.

Genetic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of cardiomyopathy is rarely present at birth and, in some individuals, may never manifest. Related individuals who carry the *same* variant may differ in the severity and rate of progression of cardiac dysfunction and associated rhythm disorders, indicating the important role of other genetic, epigenetic, and environmental modifiers in disease expression. Sex appears to play a role, as penetrance and clinical severity may be greater in men for most cardiomyopathies. The clinical course of a patient usually cannot be predicted based on which variant is present; thus, current therapy is based on the phenotype rather than the genetic defect. Currently, the greatest utility of genetic testing for cardiomyopathy is to inform family evaluations. However, genetic testing can provide risk stratification in some forms of cardiomyopathy and occasionally enables the detection of a disease for which specific therapy is indicated, such as the replacements for defective metabolic enzymes in Fabry's disease and Gaucher's disease. Moreover, clinical trials are interrogating the role of gene therapies for cardiomyopathy, which will provide greater impetus for genetic testing.

FURTHER READING

- ARBELO E et al: 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J* 44:3503, 2023.
- ELLIOTT P: Towards a new classification of cardiomyopathies. *Curr Cardiol Rep* 25:229, 2023.
- KONTOROVICH AR: Approaches to genetic screening in cardiomyopathies: Practical guidance for clinicians. *JACC Heart Fail* 11:133, 2023.
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TABLE 267-1 Selected Genetic Defects Associated with Cardiomyopathy

	GENE PRODUCT	INHERITANCE	CARDIAC PHENOTYPE	ISOLATED CARDIAC PHENOTYPE ^a	EXTRACARDIAC MANIFESTATIONS
Sarcomere	<i>ACTC1</i> (cardiac actin)	AD	HCM, DCM	Yes	
	<i>MYH7</i> (β myosin heavy chain)	AD	HCM, DCM, LVNC	Yes	Skeletal myopathy
	<i>MYBPC3</i> (myosin binding protein C)	AD	HCM	Yes	
	<i>TNNT2</i> (cardiac troponin T)	AD	HCM, DCM, LVNC	Yes	
	<i>TNNI3</i> (cardiac troponin I)	AD, AR	HCM, DCM, RCM	Yes	
	<i>TTN</i> (Titin)	AD	DCM	Yes	
	<i>TPM1</i> (α-tropomyosin)	AD	HCM, DCM	Yes	
	<i>TNNC1</i> (cardiac troponin C)	AD	DCM	Yes	
	<i>MYL2</i> (myosin regulatory light chain)	AD	HCM	Yes	Skeletal myopathy
	<i>MYL3</i> (myosin essential light chain)	AD	HCM	Yes	
Z-disk and cytoskeleton	<i>DES</i> (desmin)	AD	RCM, DCM	Yes	Skeletal myopathy
	<i>FLNC</i> (filamin C)	AD	DCM	Yes	Skeletal myopathy
	<i>NEXN</i> (nexilin)	AD	DCM	Yes	
	<i>VCL</i> (vinculin)	AD	DCM	Yes	
Nuclear membrane	<i>LMNA</i> (lamin A/C)	AD, AR	CDDC	Yes	Skeletal myopathy
	<i>EMD</i> (emerin)	X-linked	CDDC	No	Skeletal myopathy, contractures
Excitation-contraction coupling	<i>PLN</i> (phospholamban)	AD	DCM, ARVC	Yes	
	<i>SCN5A</i> (NAV 1.5)	AD	CDDC	Yes	Note other variants associated with Brugada syndrome
	<i>RYR2</i> (cardiac ryanodine receptor)	AD	ARVC	Yes	
	<i>CASQ2</i> (calsequestrin 2)	AR	ARVC	Yes	
	<i>PRKAG2</i> (γ-subunit of AMP kinase)	AD	HCM+	Yes	
Cellular metabolism	<i>LAMP2</i> (lysosomal associated membrane protein)	X-linked	HCM+	No ^b	Danon's disease: skeletal myopathy, cognitive impairment
	<i>TAZ</i> (tafazzin)	X-linked	DCM, LVNC	No	Barth's syndrome: skeletal myopathy, cognitive impairment, neutropenia
	<i>FXN</i> (frataxin)	AR	HCM	No	Friedreich's ataxia: ataxia, diabetes mellitus type 2
	<i>TMEM43</i> (transmembrane protein 43)	AD	ARVC	Yes	
	<i>GLA</i> (α-galactosidase-A)	X-linked	HCM+	No	Fabry's disease: renal failure, angiokeratomas and painful neuropathy
	Mitochondrial DNA	Maternal transmission	DCM, HCM	No	MELAS, MERRF, Kearns-Sayre syndrome, ocular myopathy
Sarcolemmal membrane	<i>DMD</i> (dystrophin)	X-linked	DCM	No ^b	Duchenne's and Becker's muscular dystrophy
	<i>DMPK</i> (dystrophica myotonica protein kinase)	AD	DCM	No	Myotonic dystrophy type 1
Desmosome	<i>DSP</i> (desmoplakin), <i>JUP</i> (plakoglobin)	AD, AR	ARVC, DCM	Yes	Carvajal syndrome (AR), Naxos syndrome (AR), "woolly hair" and hyperkeratosis of palms and soles
	<i>DSG2</i> (desmoglein 2), <i>DSC2</i> (desmocollin 2), <i>PKP2</i> (plakophilin 2)	AD	ARVC	Yes	
Other examples	<i>RBM20</i> (RNA binding motif 20)	AD	DCM	Yes	
	<i>BAG3</i> (BCL2-associated athanogene 3)	AD	DCM	Yes	
	<i>ALPK3</i> (α-kinase 3)	AR	HCM	Yes	

^aIndicates that the usual clinical presentation is of isolated cardiomyopathy; however, occasionally present extracardiac manifestations are also provided. ^bIndicates that isolated cardiac phenotype can occur in women with the X-linked defects.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; CDDC, conduction disease with dilated cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HCM+, HCM with preexcitation; LVNC, left ventricular noncompaction; MELAS, (mitochondrial) myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syndrome; MERRF, myoclonic epilepsy with ragged red fibers; RCM, restrictive cardiomyopathy.

The genetic architecture of hypertrophic, dilated, arrhythmogenic, and restrictive cardiomyopathy are overlapping, summarized in Table 267-1 and Fig. 267-1 and detailed in the subsequent sections organized by phenotype.

For any patient with suspected or proven genetic disease, family members should be considered and evaluated in a longitudinal fashion.

Screening generally includes both an echocardiogram and electrocardiogram (ECG). The indications and implications for confirmatory specific genetic testing vary depending on the specific variant. The profound questions raised by families about diseases shared and passed down merit serious and sensitive discussion, ideally provided by a trained genetic counselor.

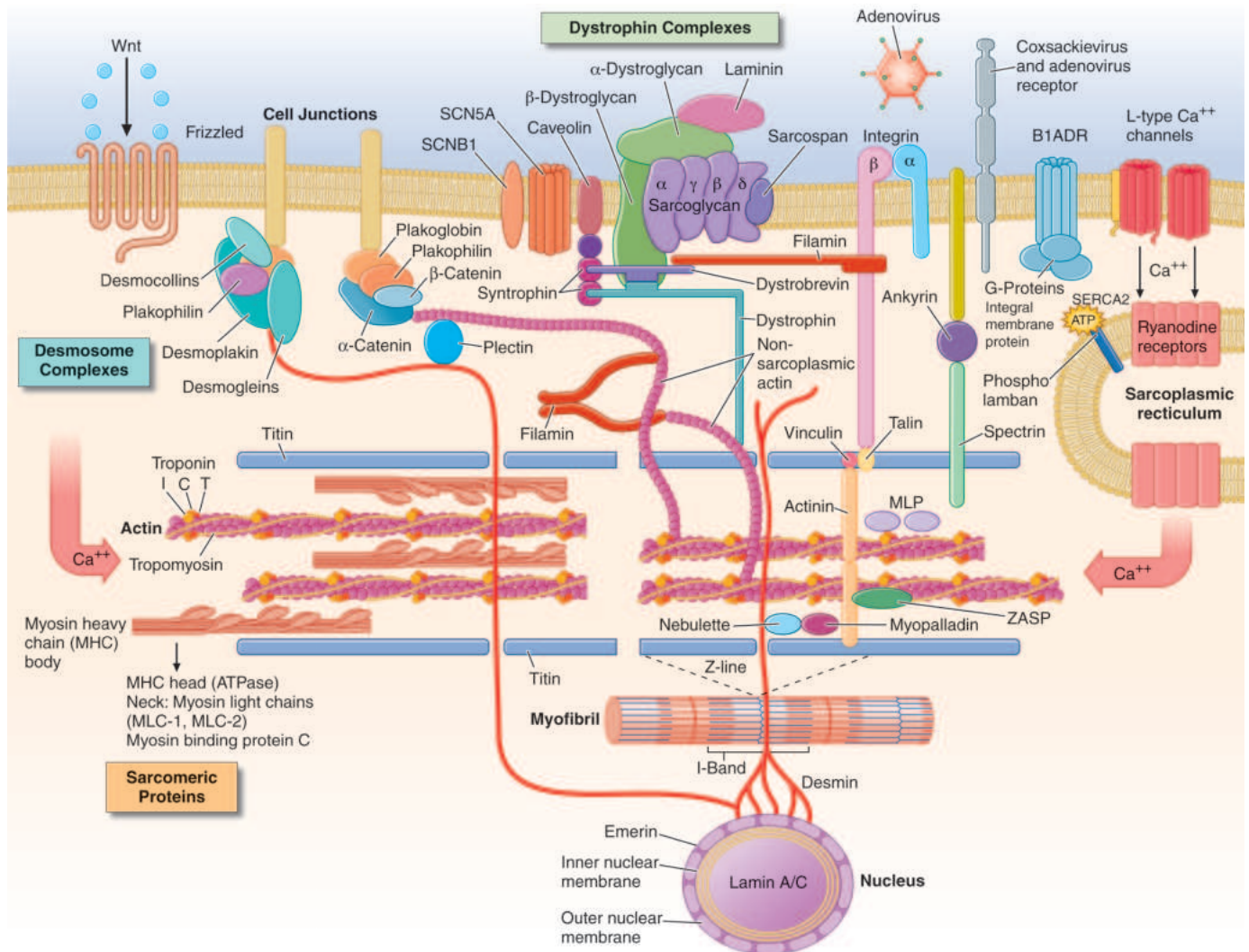


FIGURE 267-1 Drawing of myocyte indicating multiple sites of abnormal gene products associated with cardiomyopathy. Major functional groups include the sarcomeric proteins (actin, myosin, tropomyosin, and the associated regulatory proteins), the dystrophin complex stabilizing and connecting the cell membrane to intracellular structures, the desmosome complexes associated with cell-cell connections and stability, and multiple cytoskeletal proteins that integrate and stabilize the myocyte. ATP, adenosine triphosphate. (Figure adapted from Jeffrey A. Towbin, MD, University of Tennessee Health Science Center.)

HYPERTROPHIC CARDIOMYOPATHY

■ EPIDEMIOLOGY, ETIOLOGY, AND PATHOLOGY

Hypertrophic cardiomyopathy is defined as left ventricular hypertrophy that develops in the absence of causative hemodynamic factors, such as hypertension, aortic valve disease, or systemic infiltrative or storage diseases (Figs. 267-2 and 267-3). It has previously been termed *hypertrophic obstructive cardiomyopathy* (HOCM); however, the accepted terminology is now hypertrophic cardiomyopathy with or without obstruction. Prevalence in North America, Africa, and Asia is about 1:500. It is a leading cause of sudden death in the young and is an important cause of heart failure. Pediatric presentation is associated with increased early morbidity and mortality, and patients diagnosed as adults have decreased survival compared to age-matched individuals without hypertrophic cardiomyopathy.

A sarcomere gene variant is present in ~40–50% of patients with hypertrophic cardiomyopathy and is more common in those with familial disease and characteristic asymmetric septal hypertrophy. More than nine different genes with >1500 variants have been implicated, although ~80% of patients have a variant in either *MYH7* or *MYBPC3* (Table 267-1), which encode the thick myofilament of the sarcomere.

Hypertrophic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of left ventricular hypertrophy is rarely present at birth and usually develops later in life.

Women appear to have lower penetrance of sarcomere variants and an older age at hypertrophic cardiomyopathy diagnosis but subsequently increased rates of heart failure and mortality thereafter. Accordingly, screening of family members should begin in childhood, usually at adolescence, and extend through adulthood. In *MYBPC3* variant carriers, the average age of disease development is ~40 years, while 30% remain free from hypertrophy after 70 years. Related individuals who carry the *same* variant may have a different extent and pattern of hypertrophy (e.g., asymmetric vs concentric), occurrence of outflow tract obstruction, and associated clinical outcomes, although sudden death and progression to heart failure occur more commonly in families with that history.

At the level of the sarcomere, hypertrophic cardiomyopathy variants lead to enhanced calcium sensitivity, maximal force generation, and ATPase activity. Calcium handling is affected through modification of regulatory proteins. Sarcomere variants lead to abnormal energetics and impaired relaxation, both directly and as a result of hypertrophy. Hypertrophic cardiomyopathy is characterized by misalignment and disarray of the enlarged myofibrils and myocytes (Fig. 267-4), which can also occur to a lesser extent in other cardiac diseases. Although hypertrophy is the defining feature of hypertrophic cardiomyopathy, fibrosis and microvascular disease are also present. Interstitial fibrosis is detectable before overt hypertrophy develops and likely results from early activation of profibrotic pathways. In the majority of patients with overt cardiomyopathy, focal areas of replacement fibrosis can be readily

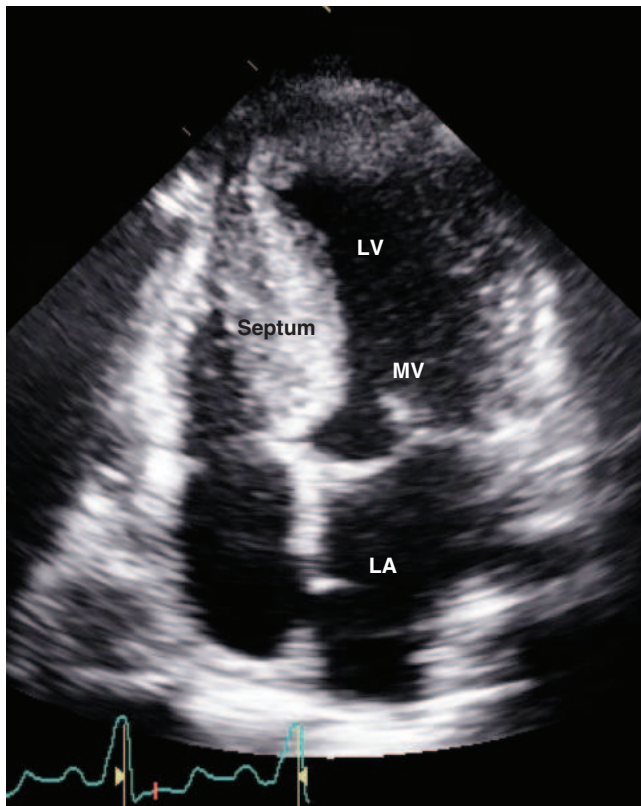


FIGURE 267-2 Hypertrophic cardiomyopathy. This echocardiogram of hypertrophic cardiomyopathy shows asymmetric hypertrophy of the septum compared to the lateral wall of the left ventricle (LV). The mitral valve (MV) is moving anteriorly toward the hypertrophied septum in systole. The left atrium (LA) is enlarged. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

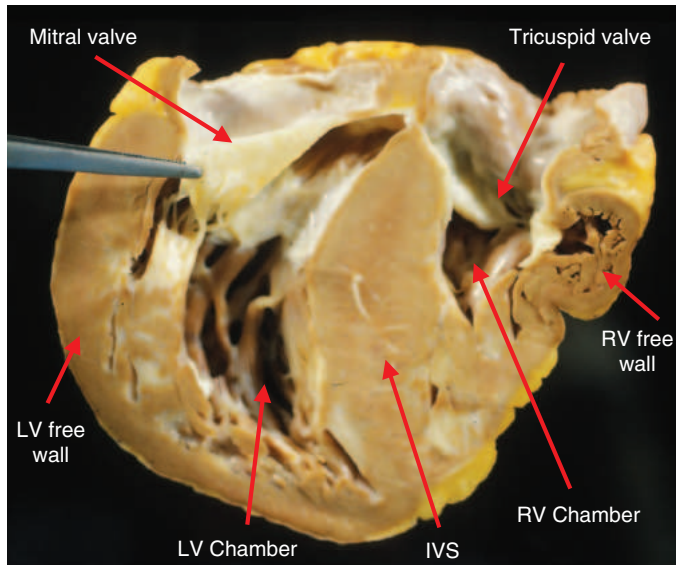


FIGURE 267-3 Hypertrophic cardiomyopathy. Gross specimen of a heart with hypertrophic cardiomyopathy removed at the time of transplantation, showing asymmetric septal hypertrophy (septum much thicker than left ventricular free wall) with the septum bulging into the left ventricular outflow tract causing obstruction. The forceps are retracting the anterior leaflet of the mitral valve, demonstrating the characteristic plaque of systolic anterior motion, manifest as endocardial fibrosis on the interventricular septum in a mirror-image pattern to the valve leaflet. There is patchy replacement fibrosis, and small thick-walled arterioles can be appreciated grossly, especially in the interventricular septum. IVS, interventricular septum; LV, left ventricle; RV, right ventricle. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

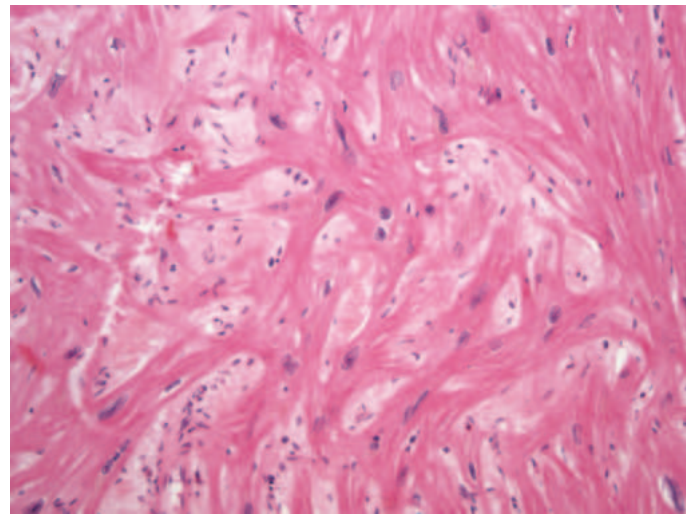


FIGURE 267-4 Hypertrophic cardiomyopathy. Microscopic image of hypertrophic cardiomyopathy showing the characteristic disarrayed myocyte architecture with swirling and branching rather than the usual parallel arrangement of myocyte fibers. Myocyte nuclei vary markedly in size, and interstitial fibrosis is present. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

detected with magnetic resonance imaging (MRI). These areas of “scar” may represent substrate for the development of ventricular arrhythmias. Increased thickness and decreased luminal area of the intramural vessels in hypertrophied myocardium contribute to microvascular ischemia and angina. Microinfarction of hypertrophied myocardium is a hypothesized mechanism for replacement scar formation.

Macroscopically, hypertrophy is typically manifest as nonuniform ventricular thickening (Fig. 267-3). The interventricular septum is the typical location of maximal hypertrophy, although other patterns of hypertrophic remodeling include concentric and midventricular. Hypertrophy confined to the ventricular apex (apical hypertrophic cardiomyopathy) is less often familial and has a different genetic substrate, with sarcomere variants present in only ~15%. Left ventricular outflow tract obstruction represents the most common focus of diagnosis and intervention, although diastolic dysfunction, myocardial fibrosis, and microvascular ischemia also contribute to contractile dysfunction and elevated intracardiac pressures. Obstruction is present in ~30% of patients at rest and can be provoked by exercise in another ~30%. Systolic obstruction is initiated by drag forces, which push an anteriorly displaced and enlarged anterior mitral leaflet into contact with the hypertrophied ventricular septum. Mitral leaflet coaptation may ensue, leading to posteriorly directed mitral regurgitation. To maintain stroke volume across outflow tract obstruction, the ventricle generates higher pressures, leading to higher wall stress and myocardial oxygen demand. Smaller chamber size and increased contractility exacerbate the severity of obstruction. Conditions of low preload, such as dehydration, and low afterload, such as arterial vasodilation, may lead to transient hypotension and near-syncope. The systolic ejection murmur of left ventricular outflow tract obstruction is harsh and late peaking and can be enhanced by bedside maneuvers that diminish ventricular volume and transiently worsen obstruction, such as the Valsalva maneuver or standing from a squatting position.

■ DIAGNOSIS

The substantial variability of hypertrophic cardiomyopathy pathology is reflected in the diversity of clinical presentations. Patients may be diagnosed after undergoing evaluations triggered by the abnormal physical findings (murmur) or by symptoms of exertional dyspnea, angina, or syncope. Alternatively, diagnosis may follow evaluations prompted by the detection of disease in family members. Cardiac imaging (Fig. 267-2) is central to diagnosis, for which the physical examination and ECG are insensitive. The identification of a disease-causing variant in a proband can focus family evaluations on variant carriers, but this strategy requires a high degree of certainty that the

variant is truly pathogenic and not a benign DNA variant. Biopsy is not recommended to diagnose hypertrophic cardiomyopathy but can be used to exclude infiltrative and metabolic diseases. Rigorous athletic training (athlete's heart) may cause intermediate degrees of physiologic hypertrophy difficult to differentiate from mild hypertrophic cardiomyopathy. Unlike hypertrophic cardiomyopathy, hypertrophy in the athlete's heart regresses with cessation of training and is accompanied by supernormal exercise capacity ($VO_{2max} > 50$ mL/kg per min), mild ventricular dilation, and normal diastolic function.

TREATMENT

Hypertrophic Cardiomyopathy

Management focuses on treatment of symptoms and prevention of sudden death and stroke (Fig. 267-5). Left ventricular outflow tract obstruction can be controlled medically in the majority of patients. β -Adrenergic blocking agents and L-type calcium channel blockers (e.g., verapamil) are first-line agents that reduce the severity of obstruction by slowing heart rate, enhancing diastolic filling, and decreasing contractility. Persistent symptoms of exertional dyspnea or chest pain can be controlled occasionally with the addition of disopyramide, an antiarrhythmic agent with potent negative inotropic properties. The recently introduced small-molecule cardiac myosin inhibitors mavacamten (U.S. Food and Drug Administration approved) and aficamten (under investigation) have shown high efficacy in the treatment of symptomatic obstructive hypertrophic cardiomyopathy, including in patients with persistent symptoms despite treatment with a beta blocker and/or those

considering septal reduction therapy. The principal risk of cardiac myosin inhibitors is a transient reduction in left ventricular ejection fraction (LVEF), which warrants frequent echocardiographic monitoring.

Patients with or without obstruction may develop heart failure symptoms due to fluid retention and require diuretic therapies for venous congestion. Severe medically refractory symptoms develop in ~5% of patients, for whom septal reduction therapy with surgical myectomy or alcohol septal ablation may be effective. Developed over 60 years ago, surgical myectomy effectively relieves outflow tract obstruction by excising part of the septal myocardium involved in the dynamic obstruction. In selected patients, perioperative mortality is extremely low with excellent long-term survival free from recurrent obstruction and symptoms. Mitral valve repair or replacement is usually unnecessary as associated eccentric mitral regurgitation resolves with myectomy alone. Alcohol septal ablation in patients with suitable coronary anatomy can relieve outflow tract obstruction via a controlled infarction of the proximal septum, which produces similar periprocedural outcomes and gradient reduction as surgical myectomy. Although head-to-head comparisons between the two septal reduction therapies do not exist, septal ablation is relegated primarily to patients who wish to avoid surgery or who have limiting comorbidities. Neither procedure has been shown to improve outcomes other than symptoms. With both procedures, the most common complication is the development of complete heart block necessitating permanent pacing. However, ventricular pacing as a primary therapy for outflow tract obstruction is ineffective and not generally advised.

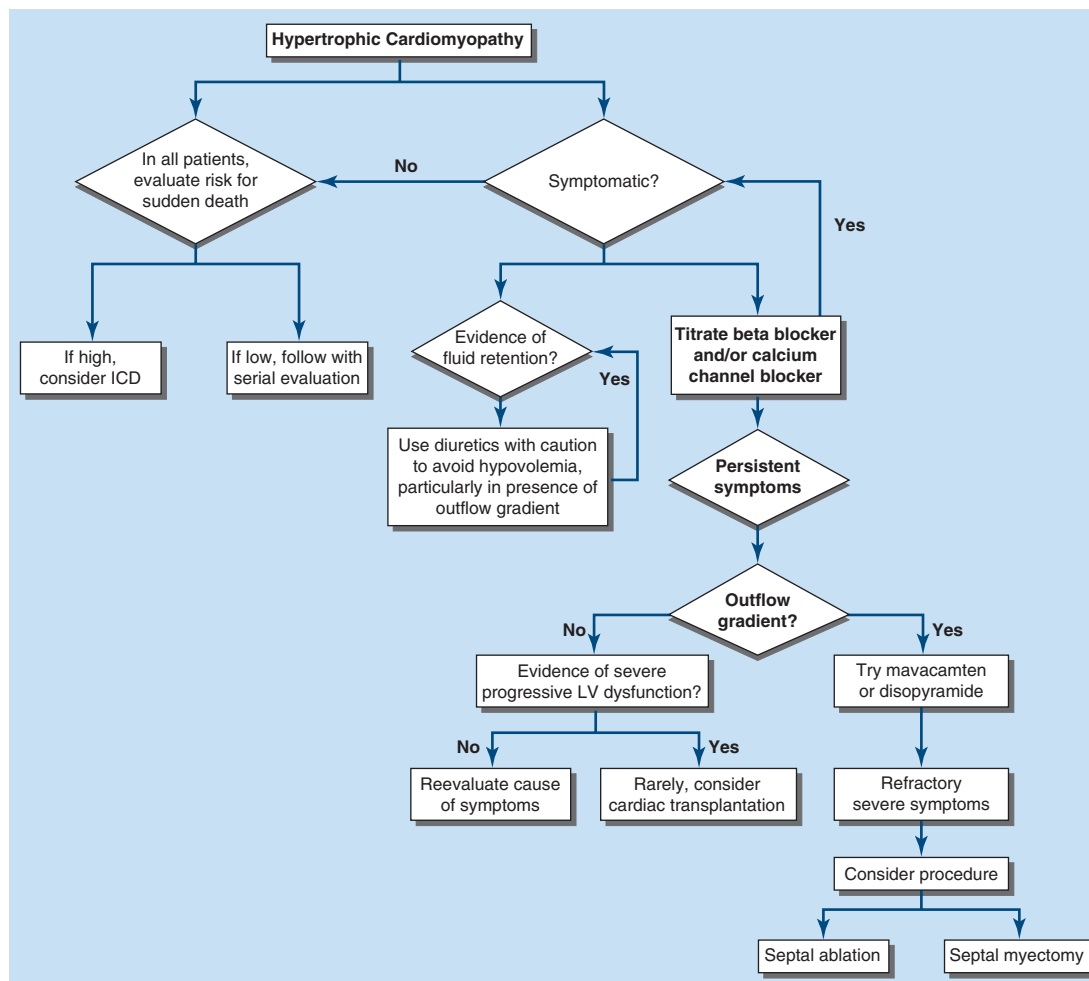


FIGURE 267-5 Treatment algorithm for hypertrophic cardiomyopathy depending on the presence and severity of symptoms and the presence of an intraventricular gradient with obstruction to outflow. Note that all patients with hypertrophic cardiomyopathy should be evaluated for atrial fibrillation and risk of sudden death, whether or not they require treatment for symptoms. ICD, implantable cardioverter-defibrillator; LV, left ventricular.

Patients with hypertrophic cardiomyopathy have an increased risk of sudden cardiac death from ventricular tachyarrhythmias. Vigorous physical activity and competitive sports have been historically prohibited; however, recent studies have failed to identify a relationship between exertion and ventricular arrhythmias in hypertrophic cardiomyopathy, empowering patients and providers to make shared decisions about exercise. Factors that increase the risk of sudden death from a baseline of 0.5% per year are presented in **Table 267-2**. As sudden death has not been reduced by medical or procedural interventions, traditionally an implantable cardioverter-defibrillator has been advised for patients with one or more major risk factors and advised on a selected basis for patient with more than one modifying risk factor. Nevertheless, the positive predictive value of most risk factors is low, and many patients receiving a defibrillator never receive an appropriate device therapy. A complementary approach to sudden death risk stratification and discussion with patients is the application of an externally validated European Society of Cardiology risk score using major criteria from **Table 267-2** and continuous variables such as outflow tract gradient and left atrial size. Shared decision-making around implantable

cardioverter-defibrillator implantation for primary prevention has emphasized discussions of estimated risk levels rather than dichotomous yes–no criteria. Long-term use of a defibrillator may be associated with serious device-related complications, particularly in young active patients. Refinement of sudden death risk through the application of contemporary technologies such as cardiac MRI is ongoing.

Atrial fibrillation is common in patients with hypertrophic cardiomyopathy and may lead to hemodynamic deterioration and embolic stroke. Rapid ventricular response is poorly tolerated and may worsen outflow tract obstruction. β -Adrenergic blocking agents and L-type calcium channel blockers slow atrioventricular (AV) nodal conduction and improve symptoms; cardiac glycosides should be avoided, as they may increase contractility and worsen obstruction. Even with adequate rate control, symptoms exacerbated by atrial fibrillation may persist due to loss of AV synchrony and may require restoration of sinus rhythm. Disopyramide and amiodarone are the preferred antiarrhythmic agents, with radiofrequency ablation considered for medically refractory cases. Anticoagulation to prevent embolic stroke in atrial fibrillation is recommended.

TABLE 267-2 Risk Stratification for Sudden Death in Hypertrophic Cardiomyopathy

MAJOR RISK FACTOR		SCREENING TECHNIQUE
History of cardiac arrest or spontaneous sustained ventricular tachycardia ^a		History
Syncope	Nonvagal, often with or after exertion	History
Family history of sudden cardiac death		Family history
Left ventricular apical aneurysm	Generally applicable to patients with apical hypertrophy	Echocardiography with contrast, cardiac magnetic resonance imaging
LV thickness >30 mm	Present in <10% of patients	Echocardiography or cardiac magnetic resonance imaging
LV systolic dysfunction (ejection fraction <50%)	Present in <10% of patients	Echocardiography or cardiac magnetic resonance imaging
Variables Utilized in the European Society of Calculator for Estimated Risk of Sudden Death		
LV outflow tract gradient	Peak gradient measured at rest or with the Valsalva maneuver, mmHg	Echocardiography
Left atrial diameter	Diameter measured in the parasternal long axis, mm	Echocardiography
LV thickness	Maximal wall thickness, mm	Echocardiography
Age		
Syncope, family history, nonsustained ventricular tachycardia	As above	As above
Modifying Risk Factors		
Late gadolinium enhancement	As a percentage of myocardial mass	Cardiac magnetic resonance imaging
Spontaneous nonsustained ventricular tachycardia	>3 beats at rate >120	Exercise or 24-h to 48-h ambulatory recording

^aImplantable cardioverter-defibrillator advised for patients with prior arrest or sustained ventricular tachycardia regardless of other risk factors if life expectancy is estimated to be >1 year. The European Society of Cardiology risk calculator can be found at <https://doc2do.com/hcm/webHCM.html> and provides an estimated 5-year risk of cardiac arrest. Patients with estimated risk of ≥6% are generally advised placement of an implantable cardioverter-defibrillator; those with risk between 4 and 6% can be considered for implant, and implant is not advised when risk is <4%. Emerging risk factors merit further clinical validation.

Abbreviation: LV, left ventricle.

■ PROGNOSIS

The general prognosis for hypertrophic cardiomyopathy is better than in early studies of referral populations, but mortality remains higher than in an age-matched population without cardiomyopathy. The sudden death risk is <1% per year; however, up to 1 in 20 patients will progress to overt systolic dysfunction with a reduced ejection fraction (<50%) with or without dilated remodeling (i.e., “burned out” or end-stage hypertrophic cardiomyopathy). These patients may suffer from low cardiac output and have an increased risk of death from progressive heart failure and sudden death unless they undergo timely cardiac transplantation.

GENETIC DILATED AND ARRHYTHMOGENIC CARDIOMYOPATHY

■ EPIDEMIOLOGY, ETIOLOGY, AND PATHOLOGY

As outlined in **Chap. 266**, an enlarged left ventricle with reduced systolic function as measured by LVEF characterizes DCM, which is considered to be present when the LVEF is ≤0.50 and/or the left ventricular diastolic dimension is >95% predicted for age and sex. In some patients with reduced LVEF, the left ventricular dilation is minimal, sometimes referred to as nondilated or minimally dilated cardiomyopathy (**Figs. 267-6, 267-7, and 267-8**).

While diverse etiologies may cause DCM and arrhythmogenic cardiomyopathy (ACM), familial clustering is present in ~30–40% of cases and monogenic etiologies can be identified in ~25%.

Sarcomere variants are most associated with hypertrophic cardiomyopathy; however, they are also implicated in DCM. The most common genetic causes of DCM are truncating variants of the giant protein titin, encoded by *TTN*, which maintains sarcomere structure and acts as a key signaling molecule.

As cytoskeletal proteins play crucial roles in the structure, connection, and stability of the myocyte, multiple defects in these proteins can lead to dilated cardiomyopathy (**Fig. 267-1**). For example, desmin forms intermediate filaments that connect the nuclear and plasma membranes, Z-lines, and the intercalated disks between muscle cells. Desmin variants impair the transmission of force and signaling for both cardiac and skeletal muscle and may cause combined cardiac and skeletal myopathy, more commonly with a restrictive phenotype (RCM) than dilated phenotype (DCM).

Defects in the sarcolemmal membrane proteins are associated with DCM. The best known is dystrophin, encoded by the X chromosome gene *DMD*, abnormalities of which cause Duchenne’s and Becker’s muscle dystrophy. This protein provides a network that supports the sarcolemma and also connects to the sarcomere. The progressive functional defect in both cardiac and skeletal muscle reflects vulnerability



FIGURE 267-6 Dilated cardiomyopathy. This gross specimen of a heart removed at the time of transplantation shows massive left ventricular dilation and moderate right ventricular dilation. Although the left ventricular wall in particular appears thinned, there is significant hypertrophy of this heart, which weighs >800 g (upper limit of normal = 360 g). A defibrillator lead is seen traversing the tricuspid valve into the right ventricular apex. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

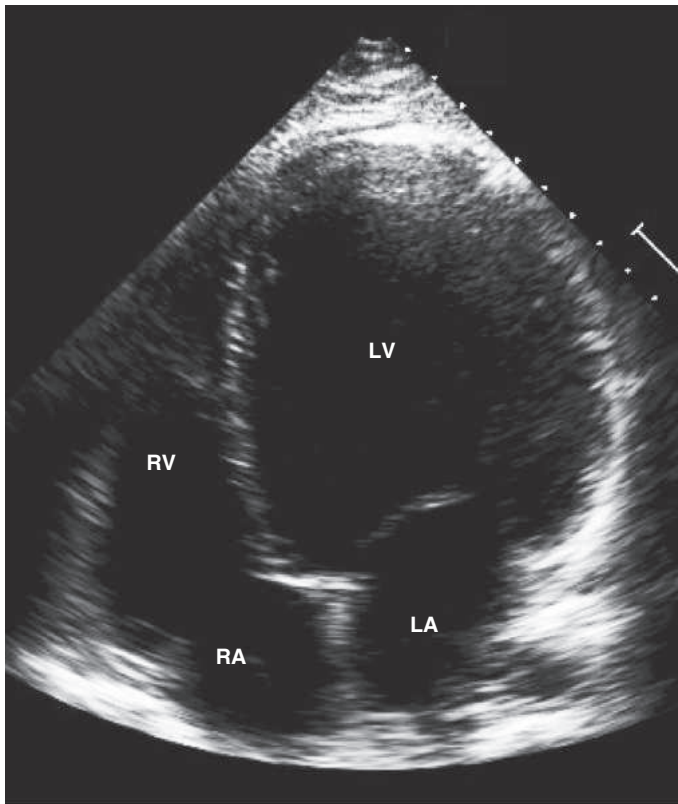


FIGURE 267-7 Dilated cardiomyopathy. This echocardiogram of a young man with dilated cardiomyopathy shows massive global dilation and thinning of the walls of the left ventricle (LV). The left atrium (LA) is also enlarged compared to normal. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. RA, right atrium; RV, right ventricle. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

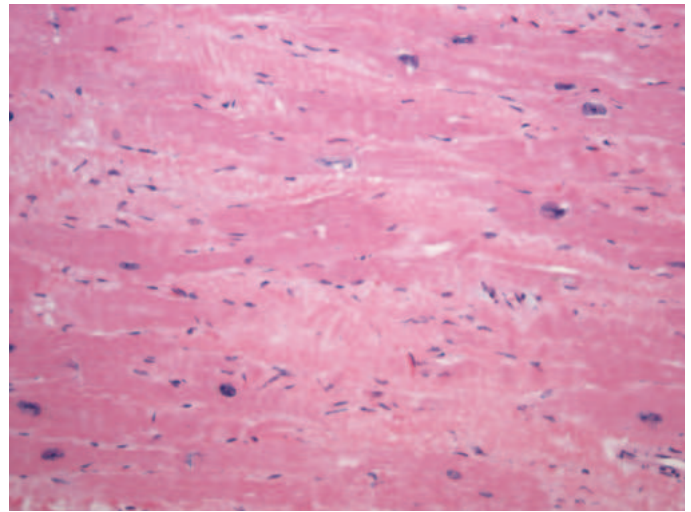


FIGURE 267-8 Dilated cardiomyopathy. Microscopic specimen of a dilated cardiomyopathy showing the nonspecific changes of interstitial fibrosis and myocyte hypertrophy characterized by increased myocyte size and enlarged, irregular nuclei. Hematoxylin and eosin-stained section, 100 $\times$ original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

to mechanical stress. Defects in the sarcolemmal channel proteins (*channelopathies*) are generally associated with primary arrhythmias, but variants in *SCN5A*, the α subunit of the Nav 1.5 ion channel protein, distinct from those that cause the Brugada or long QT syndromes, have been implicated in DCM with conduction disease.

Nuclear membrane protein defects in cardiac and skeletal muscle occur in either autosomal (lamin A/C) or X-linked (emerin) patterns. These defects are associated with a high prevalence of atrial and ventricular arrhythmias and conduction system disease, which can occur in some family members without or before detectable cardiomyopathy and underlie gene-specific risk stratification for sudden death and different utilization criteria for primary prevention implantable cardioverter-defibrillators in these patients.

Intercalated disks contribute to intracellular connections, allowing mechanical and electrical coupling between cells and also connections to desmin filaments within the cell. Variants in proteins of the desmosomal complex compromise attachment of the myocytes, which can become disconnected and die via activation of Wnt/ β -catenin and proinflammatory signaling pathways, to be replaced by fat and fibrous tissue. These areas are highly arrhythmogenic and may dilate to form aneurysms. Although more often noted in the right ventricle (arrhythmogenic right ventricular cardiomyopathy), this condition can be restricted to the left ventricle (especially when secondary to truncating variants in *DSP*, which encodes desmoplakin) or affect both ventricles and has also been termed "arrhythmogenic cardiomyopathy."

The recognized frequency of familial involvement in DCM has increased to >30%. Truncating variants in *TTN*, encoding the giant sarcomeric protein titin, are the most common cause of DCM, accounting for up to 25% of familial disease. On average, men with *TTN* truncating variants develop cardiomyopathy a decade before women, without distinctive clinical features. Variants in thick and thin filament genes account for ~8% of DCM and may manifest in early childhood.

PROGNOSIS

Prognosis and therapy of DCM and ACM are dictated primarily by the stage of clinical disease and the risk for sudden death, which also varies based on disease gene (higher for patients with variants in *DES*, *DSP*, *DSC2*, *DCG2*, *FLNC*, *LMNA*, *PKP2*, *PLN*, *RBM20*, *SCN5A*, and *TMEM43*). The rate of progression of disease is also heritable, with marked variation based on disease gene observed (e.g., patients with *TTN* truncating variants frequently experience recovery with medical therapy). Medical therapy is generally guided by the phenotype, such that patients with DCM and reduced LVEF are treated with therapies recommended for heart failure with reduced ejection fraction

(Chap. 264). As for HCM, shared decision-making is needed regarding implantable cardioverter-defibrillators. However, the specific genotype plays a greater role in decisions regarding DCM, for which some features may warrant implantable cardioverter-defibrillator placement before the LVEF has declined to 0.35, such as the presence of pathogenic *LMNA* or *FLNC* variants or a family history of sudden death at early ages.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) has an established diagnostic framework (task force criteria) that rests upon identifying and quantifying right ventricular dilation, dyskinesia, and ECG abnormalities (repolarization, depolarization, and arrhythmias) in the context of a suggestive family history of genetic test results. Overlapping with ARVC and DCM is ACM, in which ventricular arrhythmias may precede or supersede the severity of predominantly left ventricular remodeling. Unlike ARVC, consensus diagnostic criteria for ACM are lacking. Early stages of ARVC and ACM may be restricted to ventricular arrhythmias, and over years, ventricular dilation, hypokinesia, and failure may ensue. Patients with an initial presentation of right ventricular cardiomyopathy who progress to include left ventricular dysfunction are at high risk for adverse events.

CARDIOMYOPATHY DUE TO INHERITED DISORDERS OF METABOLISM

Multiple genetic disorders of metabolic pathways can cause myocardial disease, due to infiltration of abnormal products or cells containing them between the myocytes, and storage disease, due to their accumulation within cells (Table 267-1). Hypertrophic cardiomyopathy may be mimicked by the myocardium thickened with these abnormal products causing “pseudohypertrophy,” usually with an abnormally short PR interval. The pseudohypertrophic phenotype is most common, but restrictive cardiomyopathy and DCM may occur. Most of these diseases are diagnosed during childhood.

Fabry's disease results from a deficiency of the lysosomal enzyme alpha-galactosidase A caused by variants in *GLA*. This disorder of glycosphingolipid metabolism is an X-linked disorder that may also cause clinical disease in female carriers. Glycolipid accumulation may be limited to the cardiac tissues but usually also involves the skin, peripheral nerve, and kidney. Electron microscopy of endomyocardial biopsy tissue shows diagnostic vesicles containing concentric lamellar figures (Fig. 267-9). Diagnosis can be made through assessment of enzyme activity and/or *GLA* sequencing and is crucial because enzyme replacement can reduce abnormal deposits and improve cardiac and clinical function. The magnitude of clinical impact has not been well established for this therapy, which requires frequent infusions of the enzyme at a cost of >\$100,000 a year. The oral chaperone therapy, migalastat, stabilizes mutant forms of alpha-galactosidase, increases enzymatic activity, and was approved for use in a subset of patients with Fabry's disease bearing variants amenable to this therapy.

Carnitine is an essential cofactor in long-chain fatty acid metabolism. Multiple defects have been described that lead to carnitine deficiency, causing intracellular lipid inclusions and restrictive cardiomyopathy or DCM, often presenting in children. Fatty acid oxidation requires many metabolic steps with specific enzymes that can be deficient, with complex interactions with carnitine. Depending on the defect, cardiac and skeletal myopathy can be ameliorated with replacement of fatty acid intermediates and carnitine.

Two monogenic metabolic cardiomyopathies cause increased ventricular wall thickness without an increase of muscle subunits or an increase in contractility. Variants in the gamma-2 regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase important for glucose metabolism (*PRKAG2*) have been associated with a high prevalence of conduction abnormalities, such as AV block and ventricular preexcitation. Several defects have been reported in an X-linked lysosome-associated membrane protein (*LAMP2*). This defect can be maternally transmitted or sporadic and has occasionally been isolated to the heart, although it often leads to a syndrome of skeletal myopathy, intellectual disability, and hepatic dysfunction

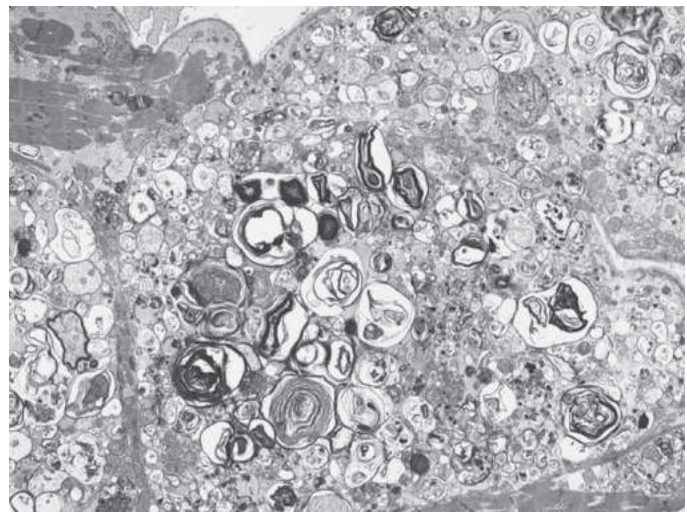


FIGURE 267-9 Fabry's disease. Transmission electron micrograph of a right ventricular endomyocardial biopsy specimen at high magnification showing the characteristic concentric lamellar inclusions of glycosphingolipids accumulating as a result of deficiency of the lysosomal enzyme alpha-galactosidase A. Image taken at 15,000× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

referred to as *Danon disease*. Extreme left ventricular hypertrophy appears early, often in childhood, and can progress rapidly to end-stage heart failure with low ejection fraction. Electron microscopy of these metabolic disorders shows that the myocytes are enlarged by multiple intracellular vacuoles of metabolic by-products. Gene therapy using a viral vector to deliver functional *LAMP2* to cardiomyocytes is currently under study in humans with Danon disease.

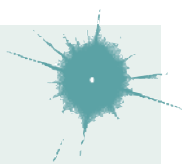
RESTRICTIVE CARDIOMYOPATHY

Most restrictive cardiomyopathy (RCM) is due to acquired causes, and there is increasing emphasis to diagnose amyloidosis due to transthyretin variants (see Chap. 266). Inherited metabolic and storage diseases can cause RCM, as can variants in *DES* causing combined cardiac and skeletal myopathy and sarcomere variants causing an overlap of RCM and hypertrophic cardiomyopathy.

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Neal K. Lakdawala,
Lynne Warner Stevenson, Joseph Loscalzo



Myocarditis is defined as inflammation of the heart muscle, which may present acutely, subacutely, or insidiously. Outcomes can include resolution, relapsing course, or progression to chronic cardiomyopathy. Myocarditis is generally considered acute when presenting with less than a month of symptoms, often only a few days. The profile of acute myocarditis is changing as the use of sensitive troponin assays and cardiac magnetic resonance imaging (MRI) are increasing recognition of mild cases with good outcomes. Acute myocarditis is most often attributed to active infection but can be caused by multiple types of noninfectious inflammation, such as sarcoidosis, giant cell and eosinophilic myocarditis, and systemic autoimmune disease or immunotherapies. It is uncertain as to how often chronic myocardial inflammation contributes to dilated cardiomyopathy. As with other cardiomyopathies, there is increasing implication of genetic predisposition to inflammatory responses and of independent pathogenic variants as primary cause of myocyte pathology, with almost one in five patients with inflammatory myocarditis harboring genetic variants considered pathogenic for cardiomyopathy.

MODELS OF INFECTIOUS MYOCARDITIS

Infectious agents can injure the myocardium through direct invasion with disruption of normal cellular processes and through activation of different phases of immune responses with or without persistent infection. Although myocarditis has been reported with most types of infectious agents, it is most often associated with viruses and the protozoal disease *Trypanosoma cruzi* (Chagas' disease). The pathogenesis of viral myocarditis has been traditionally portrayed in three phases, arising from extensive study in murine models of enteroviruses, with much less known about human infection. As defined by infection with coxsackie B virus, phase I includes direct invasion of the myocardium. Cellular entry may be enhanced by some genetic variants of the coxsackie/adenovirus receptors. The enteroviral protease A degrades the myocyte structural protein dystrophin and interacts with other proteins to induce apoptosis and interfere with autophagy. Direct myocardial invasion with entry of the viral genome has been shown to occur with the enteroviruses, HIV, and dengue virus. However, most common viruses do not appear to inflict cardiac damage directly. Early cardiac effects may result primarily from cytokine storm and other nonspecific immune responses leading to myocardial depression. This initial immune response appears to be crucial to recovery, as early immunosuppression increased viral replication and worsened cardiac injury in animal models.

The second phase is host response to infection in recognition of common antigenic patterns, triggering macrophage activation and expansion of specific T- and B-cell populations. Myocarditis due to this phase of immune response without direct viral-mediated injury is considered to be virally "triggered" myocarditis, implicated with respiratory viruses including adenovirus, influenza, and COVID-19. Molecular mimicry between viral and cardiac antigens may be the cause of some cases of myocardial injury caused by autoreactive T cells in the absence of ongoing viral infection. There is increasing study of the role of viral "hijacking" of cellular machinery to produce extracellular vesicles containing viral RNA that may then gain protected entry into other cells. A third phase of progression to chronic cardiomyopathy has been demonstrated in animal models of enteroviruses. However, myocarditis is rarely due to enteroviruses in adults. There are limited data providing direct links between chronic cardiomyopathy and previous viral infection (see "Chronic Myocarditis and Cardiomyopathy" below). The MRI pattern of intramyocardial late gadolinium enhancement

in chronic cardiomyopathy was previously considered as evidence of prior viral myocarditis, but this pattern is now recognized to be common in genetic cardiomyopathy as well.

ACUTE MYOCARDITIS

■ PRESENTATION AND DIAGNOSIS

Acute myocarditis in adults typically occurs between 30 and 45 years and is more common in men than women, who tend to present at over 45 years of age. Prodromal symptoms typical of influenza, gastroenteritis, or upper respiratory infection may have occurred days to a few weeks earlier. Fever is present in over half of cases. Chest pain is the most common symptom of acute myocarditis, occurring in >80% of patients, who also often present with dyspnea or arrhythmias. Arrhythmias can manifest as palpitations or syncope but can also cause sudden cardiac death, as in an autopsy series in which inflammatory myocarditis was diagnosed 3–10% of previously healthy young adults. At presentation, about one-fourth of acute myocarditis cases include left ventricular ejection fraction (LVEF) <0.50, ventricular arrhythmias, or clinical shock, which is reported in ~3–9% of cases and termed *fulminant myocarditis*.

Viral titers are not often helpful to guide initial therapy of acute myocarditis. Respiratory viral panels can confirm recent infection with influenza and adenovirus, most implicated in acute myocarditis in adults with a viral prodrome. Finding of COVID-19 may alert to extracardiac involvement. Specific infectious serologies for HIV, Chagas' disease, cytomegalovirus, dengue fever, and Lyme disease and serologies for systemic autoimmune disease should be sent in selected patients. Eosinophil counts should be routinely checked because hypereosinophilia is present in most cases of eosinophilic myocarditis.

The common definition for "probable myocarditis" includes new appearance of at least one symptom listed above and at least one supporting finding, which can be elevated troponin levels, consistent ECG findings, or imaging findings of decreased LVEF or obvious wall motion abnormality. Other laboratory findings may include elevated creatine phosphokinase levels, indicating cardiac or skeletal muscle involvement, and elevated C-reactive protein levels. The most common electrocardiogram (ECG) findings are ST elevation suggesting infarction, but also include conduction block, tachyarrhythmias, and nonspecific ST-T changes. Because the combination of chest pain, ECG changes, and elevated troponin is typical of both acute myocarditis and myocardial infarction, the first step in the differential diagnosis is often coronary artery imaging. Subsequent diagnosis of acute myocarditis has been reported in up to one-third of patients with myocardial infarction and nonobstructed coronary arteries (MINOCA).

"Definite myocarditis" previously required positive biopsy findings of typical inflammatory lymphocytic infiltrate on myocardial biopsy (Fig. 268-1).

Newer techniques of immunohistochemistry may increase sensitivity of biopsies and advance our understanding of the inflammatory cell populations. However, the diagnosis can now be confirmed noninvasively when typical symptomatic presentation is accompanied by combination of elevated troponin levels and consistent findings on MRI, which include evidence of both myocardial edema and nonischemic myocardial injury in the absence of other known cause (Fig. 268-2).

Although cardiac MRI may often be sufficient to diagnose acute myocarditis, endomyocardial biopsy should be performed when ventricular arrhythmias, conduction block, elevated eosinophil count, or evidence of systemic autoimmune disease suggests causes of acute myocarditis with specific implications for therapy and prognosis, as discussed below in "Noninfective Inflammatory Myocarditis."

■ THERAPY AND OUTCOMES

The prognosis is good for "uncomplicated" acute myocarditis, presenting with LVEF ≥0.50 without ventricular arrhythmias or circulatory shock. In the largest series, this low-risk group accounted for about three-fourths of patients with acute myocarditis, in which spontaneous recovery was common without specific therapies other than diuretics and nonsteroidal analgesics for chest pain. Almost all of these patients

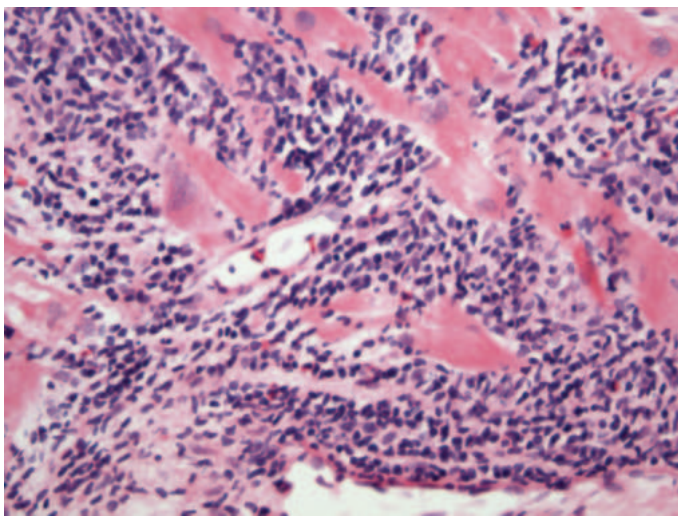


FIGURE 268-1 Acute myocarditis. Microscopic image of an endomyocardial biopsy showing massive infiltration with mononuclear cells and occasional eosinophils associated with clear myocyte damage. The myocyte nuclei are enlarged and reactive. Such extensive involvement of the myocardium would lead to extensive replacement fibrosis even if the inflammatory response could be suppressed. Hematoxylin and eosin–stained section, 200× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

still had LVEF ≥ 0.50 on follow-up imaging and survived without transplantation at 5 years of follow-up. In the one-fourth of patients with complicated presentations, ~18% died or underwent heart transplantation in the next 5 years. Patients with reduced LVEF are generally discharged on the recommended therapies for heart failure with reduced ejection fraction (HFrEF). There are no data supporting routine immunosuppression in patients with acute myocarditis with presumed viral etiology. Fulminant myocarditis requiring high-dose inotropic therapy or mechanical circulatory support occurs in 3–9% of acute myocarditis, with early outcomes of refractory cardiogenic shock but recovery to near-normal LVEF in >50% of affected patients.

CHRONIC MYOCARDITIS AND CARDIOMYOPATHY

Patients with reduced LVEF at the time of presentation with acute myocarditis are at higher risk of developing chronic cardiomyopathy. When the LVEF does not resolve in the initial months after diagnosis,

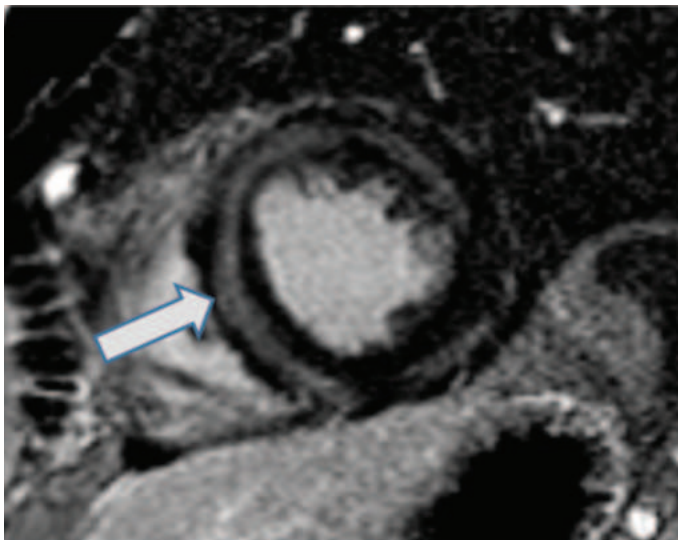


FIGURE 268-2 Magnetic resonance image of myocarditis showing the typical mid-wall location (arrow) for late gadolinium enhancement from cardiac inflammation and scarring. (Image courtesy of Ron Blankstein, MD, and Marcelo Di Carli, MD, Division of Nuclear Medicine, Brigham and Women's Hospital, Boston.)

particularly with persistent elevation of troponin, cardiac magnetic resonance imaging (CMRi) or endomyocardial biopsy may reveal ongoing inflammation and developing fibrosis. Evaluation should again be considered for specific etiologies of myocarditis including noninfectious causes of inflammatory disease and for other causes of dilated cardiomyopathy (**Chap. 266, Table 266-2**).

Evidence of chronic inflammatory disease may also be found in some patients presenting with gradual onset of dilated cardiomyopathy without prior acute myocarditis. Immunosuppression for nonspecific lymphocytic myocarditis in the chronic setting has been tried in multiple series but has not demonstrated convincing benefit. Additional findings of anticardiac antibodies and viral genome fragments are of uncertain significance, as they could be either causes of ongoing cardiac injury or neutral bystanders. Assay for anticardiac antibodies and viral genome analysis in chronic cardiomyopathy continue to be investigated but are not in routine clinical use.

In the past, dilated cardiomyopathy without other cause was generally assumed to result from previously unrecognized viral myocarditis, in part because CMRi patterns of fibrosis suggested prior inflammation. However very similar patterns are typical of genetic cardiomyopathies. The expanding access to genetic testing reveals that 20–40% of patients with dilated cardiomyopathy have pathogenic variants sufficient to cause their cardiomyopathy, and the prevalence and nature of these variants are similar in acute myocarditis. Mapping of the interconnections between genetic predisposition, inflammation, and cardiomyopathy is evolving rapidly.

SPECIFIC CAUSES OF INFECTIOUS MYOCARDITIS

The first viruses implicated in infectious myocarditis were the picornavirus family of RNA viruses, principally the enteroviruses, coxsackie virus, echovirus, and poliovirus. Influenza, another RNA virus, is implicated with varying frequency every winter and spring as epitopes change. Of the DNA viruses, adenovirus, vaccinia, and the herpesviruses (varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 [HHV6]) can cause myocarditis but also occur commonly in the healthy population. Polymerase chain reaction (PCR) detects viral genomes in some patients with dilated cardiomyopathy and persistent lymphocytic infiltrates defined as “chronic myocarditis,” such as the DNA viruses parvovirus B19 and HHV6, but these are also found in normal “control” hearts, so their contribution to chronic cardiomyopathy is uncertain.

COVID-19 is an RNA virus for which infection was associated with substantial rates of cardiac involvement in patients hospitalized with severe disease, including acute coronary syndrome, thromboemboli, pericarditis, and myocarditis, for which the diagnosis was limited to clinical findings and elevated enzymes rather than demonstration of lymphocytic infiltrates, as biopsies were rarely performed. From broad population data, the rate of myocarditis during the pandemic was estimated at 150/100,000 people, a 15-fold increase over pre-COVID incidence. As for most causes of viral myocarditis, the most common adult patients are young men under the age of 40. As for other viruses, there are multiple potential mechanisms of cardiac injury. Viral particles were identified by PCR in myocardial samples but in low levels at which pathogenicity was uncertain. Other mechanisms include cytokine storm, activated T cells and macrophages, and potential molecular mimicry by which autoimmune reactions may be triggered, as for some animal models of myocarditis with other viruses. As with multiple other viruses, extracellular vesicles containing viral RNA have been identified in myocardium during COVID infection, potentially promoting protected entry into other cells for further injury. In addition, the endothelium is also vulnerable, leading to prothrombotic endotheliopathy that may contribute to myocardial ischemia and stroke, along with the systemic coagulopathy.

HIV was associated with a dilated cardiomyopathy incidence of 1–2%, but this is declining with the availability of highly active antiretroviral therapy. Cardiomyopathy in HIV may also result from other associated viruses, such as cytomegalovirus and hepatitis C. Antiviral drugs to treat chronic HIV can cause cardiomyopathy, both directly

and through drug hypersensitivity. The clinical picture may be complicated by pericardial effusions and pulmonary hypertension. There is an increased frequency of lymphocytic myocarditis found at autopsy; HIV viral particles have been demonstrated in the myocardium in some cases.

For any serious infection, the systemic inflammatory response can cause nonspecific depression of cardiac function, which is generally reversible if the patient survives. Other viruses implicated specifically in myocarditis include mumps, respiratory syncytial virus, the arboviruses (dengue fever and yellow fever), and arenaviruses (Lassa fever).

■ OTHER INFECTIOUS CAUSES

Parasitic Myocarditis Chagas' disease is the third most common parasitic infection in the world and the most common infective cause of cardiomyopathy. The protozoan *T. cruzi* is transmitted by the bite of the reduviid bug, endemic in the rural areas of South and Central America. Transmission can also occur through blood transfusion, organ donation, from mother to fetus, and occasionally orally. Programs to eradicate the insect vector have decreased the global prevalence from about 18 million in 1990 to 6 million, with the highest number of cases in Brazil and Argentina and increased prevalence also in Spain. It is estimated that >300,000 residents in the United States are infected with Chagas' disease, a minority of whom have acquired it locally.

Initial infection with *T. cruzi* is usually silent but, in 5–10% of cases, can present with systemic illness and acute myocarditis with systemic dense parasitic infiltration in the myocardium forming pseudocysts that rupture and lead to diffuse myocyte necrosis. After initial infection, patients enter an "indeterminate phase," which can last for decades. The silent progression during this phase was at one time attributed to secondary immune activation, but a degree of persistent parasitemia can now be detected and is recognized as the major determinant of ongoing inflammation and progression to chronic heart failure. Depopulation of parasympathetic neurons in the heart and gastrointestinal tract likely contributes to clinical disease. Understanding of the disease patterns has improved in part from the ability to test blood donors for infection. Better detection of the organism has revealed that both the prevalence and survival of patients in the indeterminate phase are higher than previously recognized, with over half of patients remaining asymptomatic.

T. cruzi infection should be considered during evaluation of acute myocarditis or cardiomyopathy in all patients from endemic regions and for other patients with suggestive features. These include sinus and atrioventricular node conduction system disease and right bundle branch block, with frequent atrial and ventricular arrhythmias, some of which may cause sudden death before symptomatic disease. The dilated ventricles are thrombogenic and sometimes have aneurysms. For acute myocarditis, PCR is the most sensitive test and trypomastigotes may also be detected in blood when parasite levels are high. In the chronic phase with low parasite burden, multiple serologic tests may be necessary for diagnosis, but their sensitivity and specificity are improving.

Antiparasitic treatment with nifurtimox or benznidazole is recommended for acute myocarditis with Chagas' cardiomyopathy. During the indeterminate phase prior to clinical symptoms, therapy is widely recommended for children. For the indeterminate phase, there is controversy over the routine use of antiparasitic treatment, which is associated with significant toxicity. Therapy is more often advocated for patients <50 years old, who are more likely to tolerate chronic suppressive therapy. Treatment is recommended for premenopausal women and for patients on immunosuppression, such as after cardiac transplantation. A large multinational trial showed no benefit for benznidazole given to patients with chronic heart failure from Chagas' cardiomyopathy. In these patients, general therapy is as indicated for other HFrEF, with increased indications for anticoagulation and for pacemaker defibrillators. Improvement of LVEF is uncommon and survival is lower than for other cardiomyopathies after the onset of overt clinical heart failure.

Trichinellosis (trichinosis) is caused by the *Trichinella* genus of nematodes (roundworms). The larvae are ingested with undercooked meat, with an initial intestinal phase after which larvae migrate into skeletal muscles, causing myalgias, weakness, and fever. Periorbital and facial edema and conjunctival and retinal hemorrhage may also be seen. Although the larva may occasionally invade the myocardium, clinical heart failure is rare and, when observed, attributed to the eosinophilic inflammatory response. The diagnosis is made from the serologies and is further supported by the presence of eosinophilia. Treatment includes anthelmintic drugs and glucocorticoids if inflammation is severe.

Bacterial Infections Most bacterial infections can involve the heart occasionally through direct invasion and abscess formation but do so rarely. More commonly, systemic inflammatory responses to severe infection and sepsis depress myocardial contractility.

Diphtheria is caused by bacillus *Corynebacterium diphtheriae*, usually presenting with an upper respiratory illness particularly affecting the pharynx, where a pseudomembrane is formed in response to the diphtheria toxin. This toxin interferes with protein synthesis in the heart and may particularly affect the conduction system. Cardiac involvement is the most common cause of death from this infection but rarely occurs with the occasional dominant cutaneous presentation. The prevalence of vaccines has shifted the incidence of diphtheria to countries without routine immunization and to older populations who have lost their immunity. The diagnosis is made from pharyngeal bacterial culture, which requires special culture media and a positive assay for the toxin but can be suspected from gram-positive rods on a Gram stain. Clinical suspicion is sufficient indication for the specific antitoxin, which should be administered as soon as possible, with higher priority than antibiotic therapy.

Streptococcal infection with β -hemolytic streptococci is most commonly associated with acute rheumatic fever and is characterized by inflammation and fibrosis of cardiac valves and systemic connective tissue, but it can also lead to a myocarditis with focal or diffuse infiltrates of mononuclear cells. Other systemic bacterial infections that can involve the heart include brucellosis, legionella, meningococcus, mycoplasma, psittacosis, and salmonellosis, for which specific treatment is directed at the systemic infection.

Tuberculosis can involve the myocardium directly as well as through tuberculous pericarditis but rarely does so when the disease is treated with antibiotics. Whipple's disease is caused by *Tropheryma whippelii*. The usual manifestations are in the gastrointestinal tract, but pericarditis, coronary arteritis, valvular lesions, and occasionally clinical heart failure may also occur. Multidrug antituberculous regimens are effective, but the disease tends to relapse even with appropriate treatment.

Tick-Borne Infections Spirochetal myocarditis has been diagnosed from myocardial biopsies containing *Borrelia burgdorferi*, which causes Lyme disease. Lyme carditis most often presents with arthritis and conduction system disease that resolves within 1–2 weeks of antibiotic treatment and is only rarely implicated in chronic heart failure. Other borrelia species carried by either ticks or lice can cause relapsing fever. Additional tick-borne illnesses associated with febrile illnesses and myocarditis include Rocky Mountain spotted fever, Q fever, and ehrlichiosis, all of which are treated with doxycycline alone or in combination with other agents.

■ NONINFECTIVE INFLAMMATORY MYOCARDITIS

Myocardial inflammation can occur in the absence of infectious causes. The paradigm of noninfective inflammatory myocarditis is cardiac transplant rejection, from which we have learned that myocardial depression can develop and reverse quickly, that noncellular mediators such as antibodies and cytokines play a major role in addition to lymphocytes, and that myocardial antigens are exposed by prior physical injury and viral infection. In the largest registry of acute myocarditis, chronic systemic inflammatory diseases were implicated in 7% of cases and in 15% of those with high-risk features.

The most commonly diagnosed noninfective inflammatory process affecting the myocardium is sarcoidosis. Sarcoidosis, as discussed in [Chap. 379](#), is a multisystem granulomatous disease most commonly affecting the lungs, but involving many organs including skin, eyes, liver, nervous system, and bones, as well as the heart. The epidemiology appears to be changing, now recognized in men and women of all races and ethnic groups, typically between 30 and 50 years old but often after the age of 50 in women. Sarcoidosis is now understood as a combination of foreign antigen presentation and a dysregulated immune response that leads to ongoing inflammation, including activated macrophages. Occupational exposures include agriculture, firefighting, metal-working, and construction work, with silica dust, pesticides, mold, and other inhaled particles as examples of implicated antigens. The occurrence of sarcoidosis is increased in family members, reflecting potential sharing of environments and of genetic variants, which have been identified in loci affecting immune responses.

Cardiac sarcoidosis often accompanies pulmonary sarcoidosis but frequently occurs without detectable lung disease. The time course, burden and activity of cardiac granulomata, and the degree of extracardiac involvement are remarkably variable. Patients may present with rapid-onset heart failure and ventricular tachyarrhythmias, conduction block, chest pain syndromes, or minor cardiac findings in the setting of pulmonary sarcoidosis, ocular involvement, an infiltrative skin rash, or a nonspecific febrile illness. Chronic sarcoidosis may go unrecognized for months or years. When ventricular tachycardia or conduction block dominates the initial presentation of heart failure without coronary artery disease, suspicion should be high for sarcoidosis as a cause of cardiomyopathy. Right bundle branch block should raise suspicion for sarcoidosis but is uncommon with other cardiomyopathies, in which left bundle branch block is more common.

The pathology of cardiac sarcoidosis often shows a spectrum from metabolically active granulomas to bland fibrosis at the sites of previous inflammation. Regional wall-motion abnormalities are common, but global ventricular function may be preserved early during mild disease. When left ventricular function is only mildly reduced, ventricular size may be near normal, sometimes described as “nondilated” or “minimally dilated cardiomyopathy.” Although occasionally listed with restrictive cardiomyopathies, sarcoidosis with a reduced ejection fraction generally has the phenotype of dilated or minimally dilated cardiomyopathy. There may be a right ventricular predominance of both dilation and ventricular arrhythmias, in which case potential diagnoses include genetic arrhythmogenic right ventricular cardiomyopathy, with which sarcoidosis shares multiple features.

Diagnosis of cardiac sarcoidosis is easiest in the presence of biopsy-proven sarcoidosis of other organs. Imaging of the heart can show regional wall motion abnormalities or small ventricular aneurysms. MRI of the heart can identify late gadolinium enhancement in a pattern of fibrosis not compatible with myocardial infarction. Computed tomography of the chest often reveals pulmonary lymphadenopathy even in the absence of clinical lung disease. Positron emission tomography (PET) of the whole chest can highlight active sarcoid lesions that are avid for glucose in heart or lung. When metabolically active adenopathy is detected, biopsy is often necessary to rule out malignancy or chronic granulomatous infections such as tuberculosis or histoplasmosis before treating with immunosuppression for sarcoidosis. The scattered granulomata of sarcoidosis are commonly missed on cardiac biopsy ([Fig. 268-3](#)).

Immunosuppression for sarcoidosis is generally initiated with glucocorticoids. Initial dosing was traditionally high but now is more often started at 30–40 mg daily or less, with early addition or substitution of steroid-sparing agents like methotrexate or mycophenolate. Third-line treatment may include tumor necrosis factor- α inhibitors or other immunomodulators under investigation. The impact of treatment is usually more apparent for suppression of arrhythmias than for improvement of markedly impaired left ventricular dysfunction. Devices are often indicated for tachyarrhythmias or for conduction disease and usually include both pacing and defibrillation capability. Patients with sarcoidosis are immunosuppressed, and their management should be supervised by an experienced multidisciplinary team.

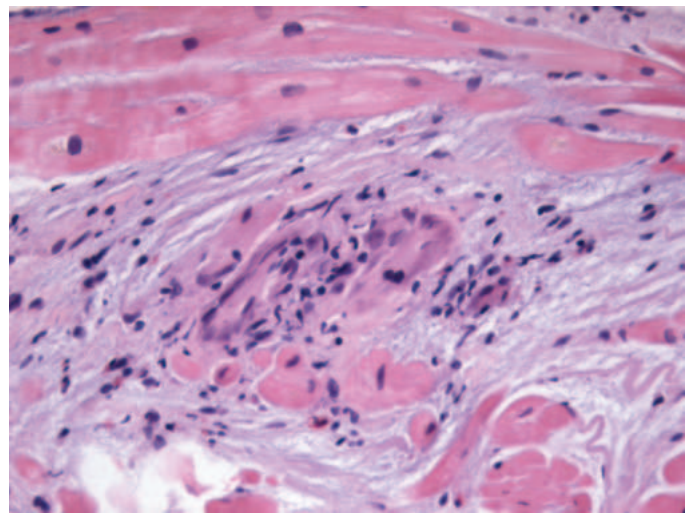


FIGURE 268-3 Sarcoidosis. Microscopic image of an endomyocardial biopsy showing a noncaseating granuloma and associated interstitial fibrosis typical of sarcoidosis. No microorganisms were present on special stains, and no foreign material was identified. Hematoxylin and eosin–stained section, 200 $\times$ original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

Cardiac sarcoidosis may respond to the initial immunosuppression course without recurrence, may fluctuate over a chronic course, or occasionally may lead to end-stage heart failure requiring heart transplantation.

Giant cell myocarditis is less common than sarcoidosis, but accounts for 10–20% of biopsy-proven myocarditis, typically presenting acutely with rapidly progressive heart failure and tachyarrhythmias. Giant cell myocarditis occurs equally in men and women, usually of older age than those with acute viral myocarditis, and is more often associated with systemic autoimmune disorders. Unlike sarcoidosis, the more diffuse involvement with giant cell myocarditis usually leads to diagnostic endomyocardial biopsy, revealing granulomatous lesions surrounded by extensive inflammation infiltrate, often with eosinophilic infiltration. However, the occasional finding of giant cell myocarditis in explanted hearts after a previous diagnosis of sarcoidosis suggests that they may share the same disease spectrum. Glucocorticoid therapy alone is rarely effective, but in combination with other immunosuppression therapies similar to those used for severe transplant rejection, the rate of death or heart transplantation has decreased for patients who are stable at the time of presentation. Most patients presenting with cardiogenic shock from giant cell myocarditis progress to need urgent mechanical support or transplantation, for which they may be rendered ineligible by severe infection resulting from intensive immunosuppression.

Eosinophilic myocarditis is one of the causes of fulminant myocarditis but may be missed on milder presentation that does not include assessment for hypereosinophilia, which is present in about three-fourths of diagnosed cases. Myocardial toxicity of eosinophils may lead to apical thrombi on cardiac imaging, and MRI reveals inflammation acutely and subendocardial fibrosis in chronic cases. Endomyocardial biopsies show infiltration with lymphocytes, neutrophils, and a high proportion of eosinophils. Hypersensitivity to chronic medications accounts for up to one-third of cases and is often cured by withdrawal of the agent and acute steroid therapy. Particularly in Mediterranean and African countries, hypereosinophilia can result from chronic parasitic infection, for which treatment may cure the myocarditis. About 12% of cases are due to eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), which responds to immunosuppression but may have a relapsing course. The hypereosinophilic syndrome (HES) accounts for 10–15% of cases, resulting from myeloproliferative variants or overproduction of eosinophil production, for which combined immunosuppression may soon include therapies under investigation to decrease eosinophil production. About 30% of HES cases are currently

unexplained. Without curative therapy, the initial inflammatory necrosis can lead to thrombosis, valve disease, and progressive endomyocardial fibrosis with restrictive physiology, termed *Loeffler endocarditis*, which presents as a restrictive cardiomyopathy.

Myocarditis is often associated with systemic inflammatory diseases, such as *polymyositis* and *dermatomyositis*, which can affect cardiac as well as proximal skeletal muscle and are usually diagnosed from autoantibodies. Myocarditis with lymphocytic infiltrates on endomyocardial biopsy can be seen in some patients with systemic lupus erythematosus, but multiple cardiac manifestations also include accelerated coronary artery disease, valvular involvement from sterile endocarditis, pericarditis, vasculitis, and chloroquine cardiotoxicity.

Vaccines have occasionally been implicated in myocarditis. This has been best studied after the smallpox vaccine in military populations. As this is a live vaccine, it is unclear whether this is direct injury, but it is generally assumed to be a hypersensitivity response. More recent concern relates to COVID-19 vaccines, after which the overall rate of myocarditis is estimated to be about 1/100,000 vaccine doses (increased to 2–3/100,000 for recipients age 18–39 years). Most cases of vaccine-induced myocarditis resolve without hospitalization. Male adults under 40 are at highest risk of myocarditis from the COVID-19 vaccines, as they are for primary infectious myocarditis after COVID-19 and other viruses. The risk for men under 40 increases after repeat COVID-19 vaccines, for which the benefit/risk for individuals should be considered.

The most dramatic form of noninfectious inflammatory myocarditis is that seen with combined immune checkpoint inhibitors. Targeted monoclonal antibody therapy to unblock the host immune response has produced remarkable remission of multiple advanced tumors. Inhibitory receptors on T lymphocytes (such as CTLA-4 and PD-1) and the programmed death ligands, such as PD-L1, interact in normal self-regulation to inhibit overactivation of immune responses. Tumor cells can upregulate these ligands to hide from immune recognition. Therapeutic antibodies against these inhibitory receptors or ligands can heighten host defenses against the tumor but also unleash immune attack against host tissues expressing PD-L1, which include skeletal and cardiac muscle, endothelial cells, and multiple other organs, such as lung, liver, pancreas, thyroid, and skin. With cardiac involvement, troponin is often elevated, B-type natriuretic peptide may be elevated, and creatine phosphokinase may be high, particularly with skeletal involvement. The diagnosis should be suspected immediately with acute cardiac presentation in patients treated with checkpoint inhibitors. Admission to the coronary care unit is currently recommended for an elevated troponin levels and ECG changes, which may be nonspecific but can also include conduction blocks and bizarre arrhythmias. Echocardiography may suggest myocardial edema, but initial ejection fraction may not be markedly reduced. Initial care should generally not be delayed for endomyocardial biopsy, which typically shows extensive lymphocytic infiltration. Patients may also present initially with other acute organ system involvement, which warrants urgent multidisciplinary management in intensive care. Therapy with high-dose glucocorticoids should be initiated rapidly and may be followed soon by more targeted immune inhibition. Reports of fatality in checkpoint inhibition myocarditis were initially very high, but outcomes are improving with earlier recognition and therapy.

■ FURTHER READING

- AMMIRATI E et al: Management of acute myocarditis and chronic inflammatory cardiomyopathy. *Circ Heart Failure* 13:e007405, 2020.
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- FAIRWEATHER D et al: COVID-19, myocarditis and pericarditis. *Circ Res* 132: 1302, 2023.
- MOSLEHI J, SALEM JE: Immune checkpoint inhibitor myocarditis treatment strategies and future directions. *JACC CardioOncol* 4:704, 2022.

269 Dilated Cardiomyopathies

Neal K. Lakdawala, Lynne Warner Stevenson,
Joseph Loscalzo

As described in [Chap. 266](#), the phenotype of dilated cardiomyopathy (DCM) is characterized by decreased left ventricular systolic function, typically with increased left ventricular dimensions, although dilation may be minimal in some cases. Multiple causes and contributing factors have been implicated ([Table 269-1](#)).

As discussed in [Chaps. 267 and 268](#), many cases are attributed to prior myocarditis, and an increasing number are associated with pathogenic genetic variants, but other causes include toxic and metabolic disorders and peripartum cardiomyopathy, which are discussed in this chapter, along with takotsubo cardiomyopathy, which has a distinct presentation and phenotype that often resolves.

Despite the multiple etiologies and variable initial presentations, DCM often progresses into a convergent clinical phenotype similar to that of other injury such as acute myocardial infarction. Some myocytes may die early in the course, while others survive only to have later programmed cell death (apoptosis), and remaining myocytes develop hypertrophy in response to increased wall stress. Local and circulating neurohormonal factors stimulate deleterious secondary responses that contribute to progression of disease. Dynamic remodeling of the interstitial scaffolding affects diastolic function and the amount of ventricular dilation. Mitral regurgitation commonly develops as the ventricle dilates and the valvular apparatus is distorted and is commonly moderate to severe by the time heart failure is advanced. There is increasing evidence for the role of chronic inflammation in disease progression even when not initially implicated. Many cases that present “acutely” have progressed silently through these stages of injury over months to years. Dilation and decreased function of the right ventricle may result directly from the initial injury but more often develop later in response to elevated afterload presented by secondary pulmonary hypertension and in relation to mechanical interactions with the failing left ventricle.

The secondary responses are often modifiable or reversible. Almost a third of patients with recent-onset cardiomyopathy in the absence of coronary artery disease demonstrate substantial spontaneous recovery to normal ejection fraction. Partial recovery to left ventricular ejection fraction (LVEF) >0.40 (“heart failure with improved ejection fraction”) is common in chronic DCM during recommended therapy with neurohormonal modulation, cardiac resynchronization therapy for left bundle branch block, and diuretics as needed to maintain fluid balance, as recommended for other heart failure with reduced LVEF ([Chap. 265](#)) regardless of the initial cause of DCM. Additional aspects of diagnosis, therapy, and outcomes for specific etiologies of DCM other than the infectious, inflammatory, and genetic cardiomyopathies are discussed below.

CARDIOTOXICITY AND CARDIOMYOPATHY

Cardiotoxicity has been reported with multiple environmental and pharmacologic agents. Often these associations are seen only with very high levels of exposure or acute overdoses, in which acute electrocardiographic and hemodynamic abnormalities may reflect both direct drug effect and systemic toxicity. *Alcohol* is the most common toxin implicated in chronic DCM. Although excess consumption may contribute to >10% of cases of heart failure, including exacerbation of heart failure with structural heart disease, alcoholic cardiomyopathy is relatively rare and remains a diagnosis of exclusion. Moreover, Mendelian randomization studies have not identified a link between genetically predicated alcohol consumption and heart failure, suggesting that the population attributable risk of alcohol to the overall heart failure epidemic is modest. Alcoholic cardiomyopathy causes

TABLE 269-1 Major Causes of Dilated Cardiomyopathy (with Common Examples)**Inflammatory Myocarditis (see Chap. 268)****Infective**

- Viral (coxsackie,^a adenovirus,^a COVID-19, HIV)
- Parasitic (*Trypanosoma cruzi*—Chagas' disease, trypanosomiasis, toxoplasmosis)
- Bacterial (diphtheria)
- Spirochetal (*Borrelia burgdorferi*—Lyme disease)
- Rickettsial (Q fever)
- Fungal (with systemic infection)

Noninfective

- Granulomatous inflammatory disease
 - Sarcoidosis
 - Giant cell myocarditis
- Eosinophilic myocarditis
- Polymyositis, dermatomyositis
- Collagen vascular disease
- Checkpoint inhibitor chemotherapy
- Transplant rejection

Toxic

- Alcohol
- Catecholamines: amphetamines, cocaine
- Chemotherapeutic agents (anthracyclines, trastuzumab)
- Interferon
- Other therapeutic agents (hydroxychloroquine, chloroquine)
- Drugs of misuse (testosterone and other anabolic steroids, emetine)
- Heavy metals: lead, mercury
- Occupational exposure: hydrocarbons, arsenicals

Metabolic^a

- Nutritional deficiencies: thiamine, selenium, carnitine
- Electrolyte deficiencies: calcium, phosphate, magnesium
- Endocrinopathy
 - Thyroid disease
 - Pheochromocytoma
 - Diabetes mellitus
- Obesity
- Hemochromatosis
- Inherited metabolic pathway defects (see Chap. 267)

Familial^a (see Table 267-1)

- Cardiomyopathies without extracardiac involvement
- Cardiomyopathy with skeletal myopathy, for example:
 - Dystrophin-related dystrophy (Duchenne's, Becker's)
 - Mitochondrial myopathies (e.g., Kearns-Sayre syndrome)
- Hemochromatosis
- Susceptibility to immune-mediated myocarditis
- Associated with other systemic diseases

Miscellaneous (Shared Elements of Above Etiologies)

- Arrhythmogenic ventricular cardiomyopathy
- Peripartum cardiomyopathy
- Left ventricular noncompaction^a
- Tachycardia-related cardiomyopathy
 - Supraventricular arrhythmias with uncontrolled rate
 - Very frequent nonsustained ventricular tachycardia or high burden of premature ventricular complexes

^aSome specific cases can be linked now to specific genetic mutation in a familial cardiomyopathy; others with similar phenotypes that appear to be acquired or idiopathic may represent genetic factors not yet identified.

many more hospital admissions in men than women, but prevalence is similar between men and women with alcoholism, with left ventricular dysfunction detected in about a third of asymptomatic patients. Estimates of the alcohol intake necessary to cause cardiomyopathy have been 3–4 ounces or ≥ 60 –80 g of pure ethanol daily for ≥ 5 years, about 750 mL of wine, 6 beers, or a half pint of hard liquor, although women may develop cardiomyopathy with lower amounts of consumption. Frequent binge drinking may also be sufficient. Toxicity is attributed both to alcohol and to its primary metabolite, acetaldehyde. Chronic heavy exposure may cause neurohormonal activation and alter metabolism, protein synthesis, substrate utilization, and oxidative stress. Polymorphisms of the genes encoding alcohol dehydrogenase and the angiotensin-converting enzyme may influence the likelihood of alcoholic cardiomyopathy. Superimposed vitamin deficiencies and toxic alcohol additives are rarely implicated currently. Mutations in *TTN* and other DCM disease genes can be identified in $\sim 10\%$ of patients with presumed alcohol cardiomyopathy.

Many patients with alcoholic cardiomyopathy are fully functional in their daily lives without apparent stigmata of alcoholism. The cardiac impairment in severe alcoholic cardiomyopathy is the sum of both permanent damage and a substantial component that is reversible after cessation of alcohol consumption. Atrial fibrillation occurs commonly both early in the disease (“holiday heart”) and in advanced stages. Medical therapy includes conventional guideline-directed medical therapies with neurohormonal, mineralocorticoid receptor, and β adrenoceptor antagonists as well as sodium-glucose cotransporter 2 inhibitors with diuretics as needed for fluid management and careful attention to electrolyte repletion. Withdrawal should be supervised to avoid exacerbations of heart failure or arrhythmias and ongoing support arranged. Even with severe disease, marked improvement can occur within 3–6 months of abstinence, but the prognosis is grim if heavy alcohol consumption continues.

Cocaine, *amphetamines*, and related catecholaminergic stimulants can produce chronic cardiomyopathy as well as acute ischemia, tachyarrhythmias, malignant hypertension, aortic dissection, and stroke. Cardiac pathology reveals microinfarcts consistent with small vessel ischemia, similar to those seen with pheochromocytoma, and thrombosis secondary to endothelial dysfunction in the case of cocaine. Regular cannabis use has been linked to increased risk of atrial fibrillation, myocardial infarction, and stroke in patients with and without other known risk factors. Cannabis is not specifically implicated as a cause of cardiomyopathy in population studies but is of concern as the potency of both inhaled and edible products continues to increase.

Chemotherapy agents are the most common drugs implicated in toxic cardiomyopathy. Judicious use balances risks of the malignancy and the risks of cardiotoxicity presented not only by the drug regimens but also by the patient's cardiovascular profile and possibly genetic factors influencing myocyte response to injury. Receipt of cardiotoxic drugs or radiation may warrant designation as “stage B” heart failure, with asymptomatic changes in cardiac structure and biomarkers. Clinical recognition can be delayed as some symptoms can overlap with cancer and the prognosis with heart failure may be worse than for the underlying cancer.

Anthracyclines (e.g., doxorubicin) cause characteristic histologic changes of vacuolar degeneration and myofibrillar loss. Multiple mechanisms have been implicated, involving reactive oxygen species and iron compounds, mitochondrial damage, transcription factors such as hypoxia-induced factor, and, most recently, inhibition of topoisomerase II involved in DNA repair. Risk for cardiotoxicity increases with older age, obesity, hypertension, diabetes mellitus, preexisting cardiac disease, higher doses or combination therapies, and left chest irradiation. Systolic dysfunction can occur acutely with symptoms of heart failure noted soon after drug administration, but more often is detected by surveillance echocardiography during the first year after exposure. Doxorubicin cardiotoxicity generally does not result in marked left ventricular dilation, such that stroke volume and systemic perfusion can be low with only a modest reduction of ejection fraction. Therapy

for reduced ejection fraction due to anthracycline therapy includes β -adrenergic receptor blockade and inhibition of the renin-angiotensin system, with conflicting data on whether these agents decrease toxicity when given in parallel with chemotherapy. The use of dexrazoxane, an intracellular iron chelating agent, can prevent anthracycline cardiomyopathy, but there is no consensus on when it should be used owing to concerns that it might attenuate the efficacy of cancer therapies. Once thought to have an inexorable downward course, many patients with symptomatic heart failure can improve to near-normal function with careful management, including prevention of “second-hit” insults such as atrial fibrillation or hypertension. The course differs for some children treated with these agents before puberty, in whom inadequate growth of the heart may lead to refractory heart failure as they reach their twenties.

Trastuzumab (Herceptin) is one of the humanized monoclonal antibodies that interfere with human epidermal growth receptor 2 (HER2), which is crucial for growth of some tumors, such as breast cancer, and for cardiac adaptation. Cardiotoxicity is highest when anthracyclines are administered in conjunction with trastuzumab; however, less toxicity is seen now when these agents are combined compared with the toxicity observed previously with paclitaxel for breast cancer. Although more often reversible than anthracycline cardiotoxicity, trastuzumab cardiomyopathy may persist in about a third of affected patients and can progress to clinical heart failure and death. For cardiotoxicity with anthracyclines or trastuzumab, therapy is recommended as for other causes of reduced ejection fraction.

Cardiotoxicity with *cyclophosphamide* and *ifosfamide* generally occurs acutely and with very high doses. 5-Fluorouracil, cisplatin, and some other alkylating agents can cause recurrent coronary spasm that occasionally leads to depressed contractility. Acute administration of interferon- α , interleukin 2, and other cytokine-based therapies can cause pericarditis, hypotension, and arrhythmias. Clinical heart failure occurring during their chronic administration usually resolves after discontinuation.

Vascular endothelial growth factor (VEGF), produced endogenously or by tumors, enhances angiogenesis by activating the VEGF signaling pathways. Monoclonal antibodies and many small-molecule *tyrosine kinase inhibitors* that affect VEGF are in use for different malignancies. Although these agents are “targeted” at specific tumor receptors or pathways, the biologic conservation of signaling pathways means that some of these drugs also find targets in the cardiovascular and other organ systems. Blood pressures increase in most patients during therapy, attributed to an imbalance between endogenous vasodilators and vasoconstrictors and alteration of glomerular function. Hypertension and proteinuria can develop with these agents, similar to preeclampsia, and presentation is associated with increased risk of future cardiac disease. Recognition of cardiotoxicity during therapy with these agents is complicated because they occasionally cause peripheral fluid accumulation (ankle edema, periorbital swelling, pleural effusions) due to local factors rather than elevated central venous pressures. Therapeutic approaches include management of associated hypertension, withdrawal of the tyrosine kinase inhibitor (when possible), and conventional treatment for heart failure. Newer tyrosine kinase inhibitors effective against multiple kinases may have more complex off-target effects. This includes the Bruton tyrosine kinase inhibitors (e.g., ibrutinib), which are used as primary therapy for lymphoid malignancies, with predominant cardiovascular risks of atrial and ventricular arrhythmias in addition to heart failure.

Proteasome inhibitors used to treat multiple myeloma are associated with an increased risk of hypertension, ischemic events, thromboembolism, and heart failure. The more potent agent, carfilzomib, appears more cardiotoxic than bortezomib. Other treatments for myeloma include immunomodulatory drugs including lenalidomide and thalidomide, which may cause heart failure in addition to risks of venous thromboembolism. Mitogen-activated extracellular signal regulated kinase (MEK) inhibitors used for metastatic melanoma may cause hypertension and cardiomyopathy, especially when co-administered with rapidly accelerated fibrosarcoma (RAF) inhibitors.

The most dramatic toxicity of contemporary cancer therapy results from combined immune checkpoint inhibitors, which block the natural counterregulatory T-cell suppression and unleash potentially fatal inflammation directed toward multiple organs that can include the heart and vessels. These are discussed in [Chap. 268](#) on noninfectious myocarditis.

Other therapeutic drugs that can cause cardiotoxicity during chronic use include tumor necrosis factor α antagonists for rheumatologic conditions, and carbamazepine, clozapine, and lithium for neurologic and psychiatric diagnoses. Antiretroviral therapies for HIV have been implicated in cardiomyopathy. Chloroquine and hydroxychloroquine, which are widely used for systemic lupus erythematosus and rheumatoid arthritis, can decrease ejection fraction with either restrictive or dilated phenotype, often in association with conduction block. The presumed mechanism of toxicity is impaired lysosomal function, with accumulation of inclusion bodies that can be seen on cardiac biopsy.

Toxic exposures can cause arrhythmias or respiratory injury acutely during accidents. Chronic exposures implicated in cumulative cardiotoxicity include cobalt, arsenicals, lead, and mercury. Treatment for these disorders includes removing exposure to the toxin and standard medical therapy for heart failure with reduced ejection fraction. Cardiomyopathy secondary to cobalt toxicity may be secondary to impaired myocardial energetics and is more common in the setting of hypothyroidism and dietary protein and thiamine deficiency. Cobalt cardiomyopathy usually presents with polycythemia, hypothyroidism, and goiter due to the effects of cobalt on red cell production and thyroxine. Most historical causes of pathologic cobalt exposure are no longer relevant (e.g., treatment of anemia associated with end-stage disease, beer foam stabilization), and recent cases have been attributed to industrial exposures and cobalt alloy prosthetic hips. Diagnosis occurs in the setting of cobalt exposure and can be confirmed by the presence of electron microscopy dense intramitochondrial particles.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy (PPCM) develops during the last trimester or within the first 5–6 months after pregnancy, most commonly within the first 2 weeks after delivery. Between 1:1000 and 1:4000 deliveries in the United States are affected. Risk factors include older maternal age, increased parity, twin pregnancy, malnutrition, and tocolytic therapy for premature labor. Up to half of cases occur in the setting of hypertensive disorders of pregnancy, including preeclampsia. Risk of PPCM is fourfold higher in black women, in whom recovery of normal LVEF takes longer and is less likely than in white women.

Several of the risk factors contribute to antiangiogenic signaling through secreted inhibitors of VEGF, such as soluble FLT1 (sFLT1), high levels of which predict worse outcome. An abnormal cleavage fragment of the nursing hormone prolactin has also been implicated in decreased vascular response during oxidative stress, and investigation is ongoing with the prolactin inhibitor bromocriptine after mixed results of small trials. Multiple other hormonal changes of pregnancy and secretory products from the placenta may interact to cause cardiac dysfunction, suggesting a “vasculohormonal model” in the development of PPCM. Genetic contribution has also been recognized. Similar to other DCM populations, truncating mutations in *TTN* are found in ~15% of cases of PPCM and associated with lower rates of recovered systolic function. Pregnancy thus represents another environmental trigger for accelerated phenotypic expression of genetic cardiomyopathy.

PPCM usually presents with evidence of congestion, and criteria generally include an LVEF ≤ 0.45 presenting toward the end of pregnancy in the absence of another cardiac diagnosis. Pregnancy can unmask previously unrecognized heart disease but usually does so by the second trimester, when the major circulatory changes have already occurred. Toward the end of pregnancy, edema and dyspnea may be mistakenly attributed to the pregnancy itself, but elevated levels of brain natriuretic peptide or troponin or evidence of elevated central venous pressures are clues to cardiac dysfunction, particularly in the setting of hypertension. Echocardiography is usually sufficient for

diagnosis, but in complex cases, cardiac magnetic resonance imaging (MRI) can be considered, but gadolinium should not be used.

Most cases of PPCM present within the first week after delivery, usually with increasing edema and dyspnea when urine output does not keep up with mobilization of fluid. Both atrial and ventricular arrhythmias can occur. It is important to exclude other complications of pregnancy such as pulmonary emboli and coronary artery dissection. Genetic testing should be considered as the results may impact the mother, in whom positive genetic testing predicts less recovery, and also other family members, too.

Initial treatment for PPCM includes loop diuretics as needed to restore normal volume status. Prior to delivery, close collaboration with the maternal-fetal medicine team is necessary to adjust therapies to stabilize the gravid mother while protecting the fetus. Digoxin and beta blockers can be used if needed for arrhythmias, and hydralazine/nitrate combinations can be used for hypertension, but renin-angiotensin system inhibitors should not be given due to adverse fetal effects. Hemodynamic instability may require ongoing hemodynamic monitoring, and plans should be in place for emergency delivery if necessary. When the mother is hemodynamically stable in the postpartum period, metoprolol tartrate, enalapril, and spironolactone have been shown to be compatible with breastfeeding. PPCM with LVEF <0.35 or marked dilation carries increased incidence of left ventricular thrombus and embolic risk, so anticoagulation is usually prescribed for the first 6 weeks once obstetric bleeding has resolved. Breastfeeding was once prohibited but now is generally encouraged in patients in whom fluid balance can be maintained through the high oral fluid intake required. For patients who are not breastfeeding, there is an ongoing large, randomized trial to determine the impact of bromocriptine on PPCM outcomes.

Improvement of LVEF to ≥ 0.50 occurs in 50–80% of PPCM, often within 6 months, when other cardiac diagnoses have been carefully excluded. Recovery is less likely with LVEF <0.30, left ventricular end-diastolic dimension ≥ 0.60 , black race, and presentation >6 weeks after delivery. Elevated levels of natriuretic peptides, troponin, and sFLT1 have also been associated with less recovery. Patients with LVEF <0.35 have a higher risk of life-threatening arrhythmias during initial presentation and early after discharge, for which consideration of wearable defibrillators is reasonable. This is burdensome both physically and psychologically to a new mother, and more data are needed to help stratify risk. One-year mortality rates after PPCM have ranged in the United States from 4% in one study to 11% in a population of black women, and have been reported as up to twofold higher in Africa.

METABOLIC CAUSES OF CARDIOMYOPATHY

Endocrine disorders affect multiple organ systems, including the heart. *Hyperthyroidism* and *hypothyroidism* do not often cause clinical heart failure in an otherwise normal heart but commonly exacerbate heart failure. Clinical signs of thyroid disease may be masked, so tests of thyroid function are part of the routine evaluation of cardiomyopathy. Hyperthyroidism should always be considered with new-onset atrial fibrillation or ventricular tachycardia or atrial fibrillation in which the rapid ventricular response is difficult to control. The most common current reason for thyroid abnormalities in the cardiac population is the treatment of tachyarrhythmias with amiodarone, a drug with substantial iodine content. Hypothyroidism should be treated with very slow escalation of thyroid supplements to avoid exacerbating tachyarrhythmias and heart failure. Hyperthyroidism and heart failure create a dangerous combination that merits very close supervision, often hospitalization, during titration of antithyroid medications, during which decompensation of heart failure may occur precipitously and fatally.

Pheochromocytoma is rare but should be considered when a patient has heart failure and very labile blood pressure and heart rate, sometimes with episodic palpitations ([Chap. 399](#)). Patients with pheochromocytoma often have postural hypotension. In addition to α -adrenergic receptor antagonists, definitive therapy requires surgical extirpation. Very high renin states, such as those caused by renal

artery stenosis, can lead to modest depression in ejection fraction with little or no ventricular dilation and markedly labile symptoms with flash pulmonary edema, related to sudden shifts in vascular tone and intravascular volume.

Controversies remain regarding whether diabetes mellitus and obesity are sufficient to cause cardiomyopathy with reduced ejection fraction. Most heart failure in diabetes mellitus results from epicardial coronary disease, with further increase in coronary artery risk due to accompanying hypertension and renal dysfunction. Cardiomyopathy may result in part from insulin resistance and increased advanced-glycosylation end products, which impair both systolic and diastolic function. However, much of the dysfunction can be attributed to scattered focal ischemia resulting from distal coronary artery tapering and limited microvascular perfusion even without proximal focal stenoses. Diabetes mellitus is a typical factor in heart failure with “preserved” ejection fraction, along with hypertension, advanced age, and female gender.

The existence of a cardiomyopathy due to obesity is generally accepted, but the overlap is not well defined with the syndrome of heart failure with preserved ejection fraction (HFpEF). In addition to cardiac involvement from associated diabetes mellitus, hypertension, and vascular inflammation of the metabolic syndrome, obesity alone is associated with impaired excretion of excess volume load, which, over time, can lead to increased wall stress and secondary adaptive neurohumoral responses. Fluid retention may be aggravated by large fluid intake and the rapid clearance of natriuretic peptides by adipose tissue. In the absence of another obvious cause of cardiomyopathy in an obese patient with systolic dysfunction without marked ventricular dilation, effective weight reduction is often associated with major improvement in ejection fraction and clinical function. Improvement in cardiac function has been described after successful bariatric surgery, although all major surgical therapy poses increased risk for patients with heart failure. Postoperative malabsorption and nutritional deficiencies, such as calcium and phosphate deficiencies, may be particularly deleterious for patients with cardiomyopathy.

Nutritional deficiencies can occasionally cause DCM but are not commonly implicated in developed countries. Beriberi heart disease due to thiamine deficiency can result from poor nutrition in undernourished populations and in patients deriving most of their calories from alcohol and has been reported in teenagers subsisting only on highly processed foods. This disease is initially a vasodilated state with very-high-output heart failure that can later progress to a low-output state; thiamine repletion can lead to prompt recovery of cardiovascular function. Abnormalities in carnitine metabolism can cause dilated or restrictive cardiomyopathies, usually in children. Deficiency of trace elements such as selenium can cause cardiomyopathy (Keshan's disease).

Calcium is essential for excitation-contraction coupling. Chronic deficiencies of calcium, such as can occur with hypoparathyroidism (particularly postsurgical) or intestinal dysfunction (from diarrheal syndromes and following extensive resection), can cause severe chronic heart failure that responds over days or weeks to vigorous calcium repletion. Phosphate is a component of high-energy compounds needed for efficient energy transfer and multiple signaling pathways. Hypophosphatemia can develop during starvation and early refeeding following a prolonged fast and occasionally during hyperalimentation.

Hemochromatosis is variably classified as a metabolic or storage disease ([Chap. 426](#)). It is included among the causes of restrictive cardiomyopathy, but the clinical presentation is often that of a DCM. The autosomal recessive form is related to the *HFE* gene. With up to 10% of the population heterozygous for one mutation, the clinical prevalence might be as high as 1 in 500. The lower observed rates highlight the limited penetrance of the disease, suggesting the role of additional genetic and environmental factors such as alcoholism affecting clinical expression. Cardiac siderosis can also be acquired from iron overload due to hemoglobinopathies in patients treated with recurrent transfusions. Excess iron is deposited in the perinuclear compartment of cardiomyocytes, with resulting disruption of intracellular architecture and

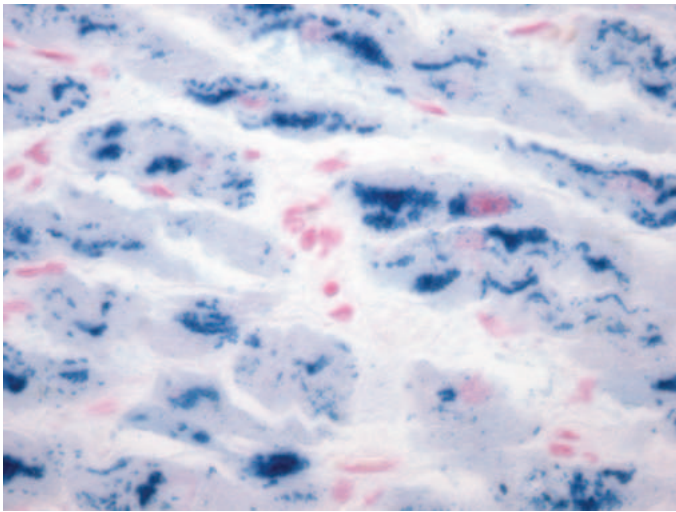


FIGURE 269-1 Hemochromatosis. Microscopic image of an endomyocardial biopsy showing extensive iron deposition within the cardiac myocytes with the Prussian blue stain (400× original magnification). (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

mitochondrial function. A diagnosis of systemic iron overload is made from measurement of serum iron and transferrin saturation, with a threshold of >60% for men and >45–50% for women. MRI is used to quantitate iron stores in the liver and heart. While endomyocardial biopsy tissue can be stained for iron (see Chap. 270 and Fig. 269-1), a diagnosis of cardiac iron overload is made principally by MRI and biopsy is not usually needed. If diagnosed early, hemochromatosis can often be managed by repeated phlebotomy to remove iron. For more severe iron overload, iron chelation therapy with desferrioxamine (deferrioxamine) or deferasirox can help to improve cardiac function if myocyte loss and replacement fibrosis are not too severe.

Inborn disorders of metabolism occasionally present with DCM, although they are most often associated with restrictive cardiomyopathy (Chap. 267, Table 267-1).

TAKOTSUBO SYNDROME OR CARDIOMYOPATHY

Apical ballooning or “takotsubo” syndrome, also referred to as stress-induced cardiomyopathy or “broken heart syndrome,” is often classified as a cardiomyopathy, although its distinct acute presentation, typical ventricular shape, and frequent rapid recovery differ from most other cardiomyopathies. It occurs typically in older women after sudden intense emotional or physical stress. The ventricle shows global ventricular dilation with basal contraction, forming the shape of the narrow-necked jar (*takotsubo*) used in Japan to trap octopuses. Originally described in Japan, it is well recognized elsewhere during emergency cardiac catheterization and intensive care unit admissions for noncardiac conditions. Presentations include pulmonary edema, hypotension, and chest pain with electrocardiogram (ECG) changes mimicking an acute infarction. The left ventricular dysfunction extends beyond a specific coronary artery distribution and generally resolves within days to weeks. Animal models and ventricular biopsies suggest that this acute cardiomyopathy may result from intense sympathetic activation with heterogeneity of myocardial autonomic innervation, diffuse microvascular spasm, and/or direct catecholamine toxicity. Cardiac MRI (Fig. 269-2) demonstrates diffuse myocardial edema without necrosis and abnormal myocardial calcium handling. Coronary angiography may be required to rule out acute coronary occlusion.

A similar picture to takotsubo can also be caused a coronary embolus in the absence of atherosclerotic coronary artery disease. No therapies have been proven beneficial, but reasonable strategies include nitrates for pulmonary edema; combined alpha and beta blockers rather than selective beta blockade if hemodynamically stable; and magnesium for arrhythmias related to QT prolongation. An intra-aortic balloon pump is occasionally employed to improve critically low cardiac output, but only if there is no left ventricular outflow tract obstruction. The long-term prognosis is generally good, with the lowest mortality associated with episodes triggered by emotional rather than physical triggers. In-hospital complications and mortality are similar to those with acute myocardial infarction. Recurrence occurs in 10% of patients at an estimated rate of 2%/year.

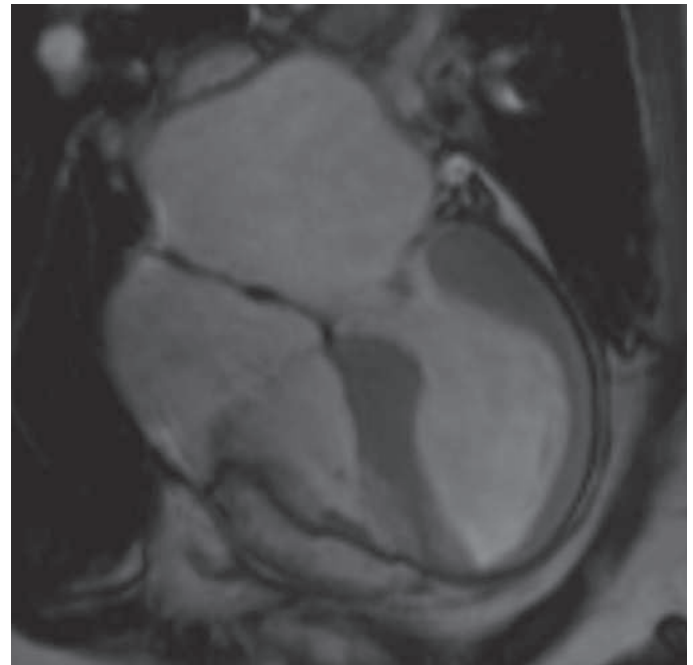
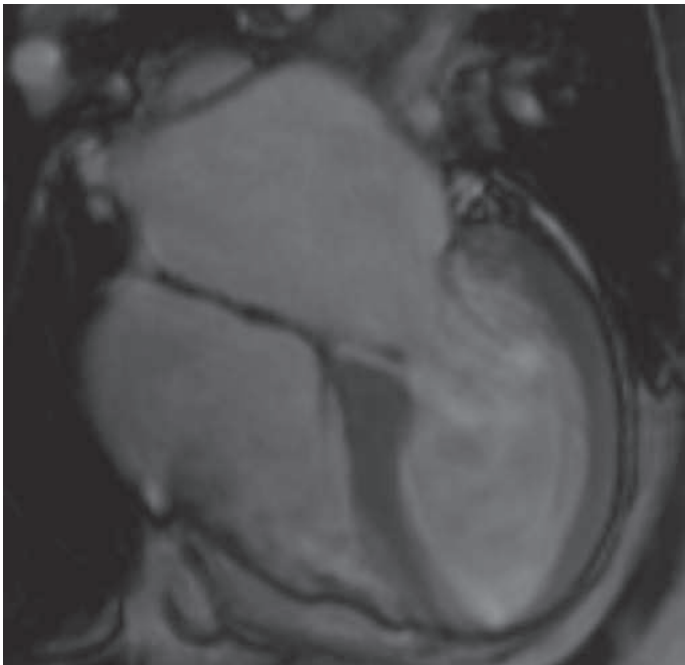


FIGURE 269-2 Takotsubo cardiomyopathy. Four-chamber view of cardiac magnetic resonance imaging demonstrating a mildly dilated left ventricle in diastole (left panel) with diffuse hypokinesis of the mid and apical segments and relative sparing of the basal segment wall motion at end systole (right panel) with left ventricular ejection fraction 46%. (Image courtesy of Raymond Kwong, MD, and Zariyat M. Mannan, MD, Cardiovascular Imaging, Brigham and Women's Hospital, Boston.)

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270 Amyloidosis and Other Restrictive Cardiomyopathies

Rodney H. Falk, Neal K. Lakdawala,
Lynne Warner Stevenson, Joseph Loscalzo

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is dominated by abnormal diastolic function within a noncompliant ventricle, often with mildly decreased contractility and ejection fraction (usually 30–50%). Both atria are enlarged, sometimes massively. Mild left ventricular dilation can be present. End-diastolic pressures are usually elevated in both ventricles, with preservation of resting cardiac output until late in the disease. Subtle exercise intolerance is usually the first symptom but is often not recognized until after clinical presentation with congestive symptoms. The restrictive diseases often present with relatively more right-sided symptoms, such as edema, abdominal discomfort, and ascites, although filling pressures are elevated in both ventricles. The cardiac impulse is less displaced than in dilated cardiomyopathy and less dynamic than in hypertrophic cardiomyopathy. A fourth heart sound is more common than a third heart sound in sinus rhythm, but atrial fibrillation is common. Jugular venous pressures often show rapid Y descents and may increase during inspiration (positive Kussmaul sign).

Most causes of RCM are “infiltrative,” due to infiltration of abnormal substances between myocytes, with the amyloidoses being the most common causes of RCM. RCM can also result from storage of abnormal metabolic products within myocytes. RCM due to acquired fibrotic injury is most commonly caused by radiation or connective tissue disease and less commonly by hypereosinophilic injury (see Chap. 268 and Table 270-1).

RCM can also be secondary to genetic causes of primary cardiomyopathy, including variants in *DES* or as a forme fruste of hypertrophic cardiomyopathy caused by sarcomere variants. The most common differential diagnosis is between RCM and constrictive pericardial disease, as both often present with dominant right-sided heart failure.

In the absence of specific therapy for the etiology of RCM, such as is now available for some patients with amyloidosis, general strategies are

TABLE 270-1 Causes of Restrictive Cardiomyopathies (RCM)

Infiltrative (Between Myocytes)

- Amyloidosis
 - Light chain (AL) amyloid
 - Familial (variant transthyretin)^a
 - Wild-type (normal) transthyretin
- Inherited metabolic defects^a

Storage (Within Myocytes)

- Hemochromatosis (iron),^a also with dilated cardiomyopathy phenotype when advanced
- Inherited metabolic defects^a
 - Fabry's disease
 - Glycogen storage disease (II, III)

Fibrotic

- Radiation
- Scleroderma

Endomyocardial

- Possibly related fibrotic diseases
 - Tropical endomyocardial fibrosis
 - Hypereosinophilic syndrome (Löffler's endocarditis)
- Carcinoid syndrome
- Radiation
- Drugs: e.g., serotonin, ergotamine

Genetic Variants Affecting Cardiomyocyte Function

- Occasional RCM due to genetic variants more commonly associated with dilated or hypertrophic cardiomyopathy
- RCM and skeletal muscle involvement with desminopathy due to pathogenic *DES* variants

^aContribution of genetic background.

focused on maintenance of optimal volume status, which is generally a compromise between adequate ventricular filling and systemic decongestion. As ventricular filling and stroke volume are often restricted, therapy with beta blockers can reduce heart rate, contractility, cardiac output, and functional reserve. Vasodilation may not be well tolerated. Other than diuretics, therapies proven effective for dilated cardiomyopathy and other heart failure with reduced ejection fraction are not recommended for routine use in RCM.

AMYLOIDOSIS

Amyloidosis is a systemic disease characterized by the deposition of fibrillar proteinaceous material primarily in the extracellular space of one or more organs. Although there are many precursor proteins that have been shown to cause amyloidosis (see Chap. 117), the unifying feature of all types of amyloid is its staining characteristics. Amyloid is a noncellular material deposited in the extracellular space that stains with Congo red and exhibits “apple-green birefringence” when viewed under polarized light microscopy. When viewed with electron microscopy, amyloid deposits are seen to consist of nonbranching fibrils ~10 nm in diameter and a few micrometers in length. From a cardiac standpoint, there are two main precursor proteins that cause most cases of amyloid cardiomyopathy: transthyretin (TTR), produced in the liver, and light chains produced by abnormal plasma cells. TTR amyloidosis may be caused by a genetic variant of TTR (ATTRv) or by wild-type TTR (ATTRwt), and variant TTR is generally considered to be less stable than wild-type TTR. Once a diagnosis of amyloidosis has been made, it is critically important to determine the precise precursor protein because treatment is specific to the type of amyloid and incorrect typing will lead to inappropriate therapy.

PATHOLOGIC MECHANISMS OF HEART FAILURE IN CARDIAC AMYLOIDOSIS

All forms of cardiac amyloidosis have a similar appearance on gross and microscopic examination (Figs. 270-1 and 270-2).



FIGURE 270-1 Gross pathology of the heart in amyloid cardiomyopathy. The left ventricle (LV) is severely thick due to amyloid infiltration. The LV cavity is small with markedly thick walls due to amyloid infiltration. The right ventricle is mildly thickened, and the left atrium (partly excised) is dilated. (Courtesy of Dr. Richard Mitchell, Brigham and Women's Hospital Department of Pathology.)

The extracellular deposits of amyloid result in an increase in the mass of the heart, due to expansion of the extracellular space. Both left and right ventricular walls demonstrate increased thickness, and decreased compliance and the left ventricular cavity may be relatively small, leading to a restrictive pathophysiology. The right ventricular cavity is often normal in size but may dilate in advanced disease. The atria are usually dilated due to the chronic elevation of biventricular diastolic filling pressure and may dilate further with the onset of atrial arrhythmias. Histologically, amyloid deposits are widespread throughout the heart so that endomyocardial biopsy is almost always diagnostic in cases of cardiac amyloidosis.

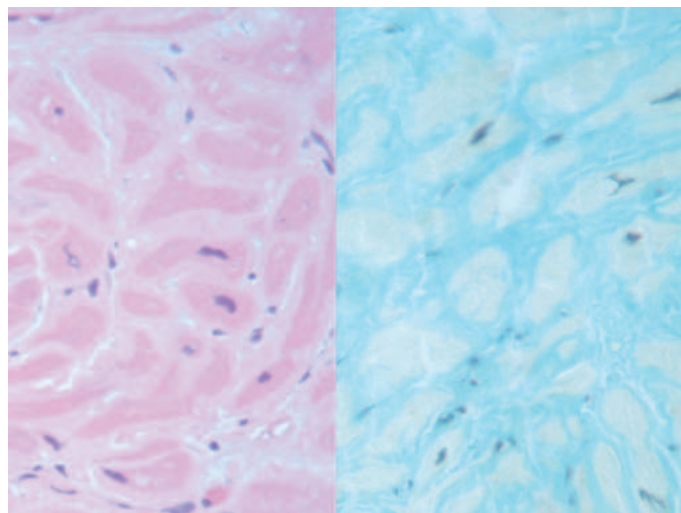


FIGURE 270-2 Histology of amyloid cardiomyopathy. Left panel: Hematoxylin and eosin stain showing extensive extracellular cardiac amyloid deposition resulting in separation and distortion of cardiomyocytes. The amyloid stains light pink and the myocytes are nucleated and stain a deeper pink. Right panel: Specimen from same patient stained with sulfated Alcian blue. The amyloid stains "sea green," and the myocytes are pale yellow-gray. Magnification $\times 60$. (Courtesy of Dr. Richard Mitchell, Brigham and Women's Hospital Department of Pathology.)

CLINICAL FEATURES OF CARDIAC AMYLOIDOSIS

There are some clinical features of light chain (AL) amyloidosis and TTR amyloidosis that suggest one or the other diagnosis, but the cardiac features are similar enough that the final diagnosis of amyloid type often relies upon precise typing of a cardiac or extracardiac tissue biopsy. The most common clinical presentation is congestive heart failure. Although both ventricles are usually heavily infiltrated by the time congestive heart failure occurs, patients tend to present with symptoms of predominant right heart failure, namely peripheral edema and, not infrequently, ascites. Despite the clinical predominance of right ventricular failure, cardiac catheterization will reveal considerable elevation of both left and right ventricular filling pressure. Atrial arrhythmia, particularly atrial fibrillation, is a common presenting feature, particularly in TTR amyloidosis, and may occur at a time when the left ventricle is only mildly thick, precipitating heart failure in a previously asymptomatic patient. The onset of atrial fibrillation may be associated with symptoms of dyspnea, often more severe than is seen in nonamyloid patients with this arrhythmia. Refractory atrial arrhythmia, whether to antiarrhythmic drugs or characterized by failure to maintain sinus rhythm after repeated ablation procedures, should raise the possibility of TTR cardiac amyloidosis, particularly if occurring in a patient in the mid-60s or older without other apparent reason for the atrial fibrillation.

Cardiovascular physical examination in the symptomatic patient with cardiac amyloidosis reveals a normal or low pulse pressure. The apex beat may be difficult to palpate but, if felt, is usually only mildly displaced. The jugular venous pressure is almost always elevated and frequently demonstrates a paradoxical rise on inspiration (Kussmaul sign). The first and second heart sounds tend to be normal. Despite congestive heart failure, a third heart sound is very rarely heard, due to the restrictive pathophysiology and its associated impairment of ventricular relaxation. Similarly, a fourth heart sound is also unusual as the infiltrated atrium is rarely able to generate much contractile pressure. Pleural effusions, primarily caused by heart failure (but occasionally aggravated by associated hypoalbuminemia from nephrotic syndrome or by the presence of pleural amyloidosis) are quite common. Cardiac murmurs due to amyloid-associated valve disease are relatively uncommon, although a tricuspid regurgitation murmur may occasionally be present. There is an association between aortic valve stenosis and TTR amyloidosis, and a murmur of aortic stenosis may be present. Whether amyloid causes aortic stenosis or simply aggravates or precipitates heart failure in a patient with unrelated aortic valve disease is unclear. In addition to the cardiovascular examination, a careful systemic physical examination is mandatory. In advanced heart failure, hepatomegaly due to congestive heart failure is common, but an unusually hard liver may represent amyloid infiltration of the liver—something that occurs in AL amyloidosis but not TTR. The blood pressure should be checked in the supine, seated, and standing positions, seeking an abnormal postural drop. If present, this likely represents associated autonomic neuropathy, which is a feature of AL amyloidosis and some forms of variant TTR amyloidosis but not wild-type TTR amyloidosis. Macroglossia or periorbital bruising, if present, strongly suggest AL amyloidosis, whereas a history of bilateral carpal tunnel syndrome or the finding of a ruptured biceps tendon points toward TTR amyloidosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a patient with biventricular failure manifesting predominantly as edema, in association with a thick left ventricle but without a history of severe hypertension, is small. Hypertensive heart disease is usually associated with left ventricular hypertrophy on the electrocardiogram (ECG), whereas this ECG finding is uncommon in amyloidosis, and it requires several years of severe uncontrolled hypertension to produce the degree of wall thickening equal to that seen in amyloidosis. While amyloidosis, particularly ATTR, can have asymmetric left ventricular thickening, the clinical distinction between hypertrophic cardiomyopathy and amyloidosis is usually fairly clear, since the former rarely presents with peripheral edema and usually has left ventricular hypertrophy (LVH) on the ECG. Other infiltrative cardiomyopathies such as Fabry disease may have typical skin

manifestations and usually LVH on the ECG. The rare mitochondrial cardiomyopathies may have an echocardiographic appearance similar to amyloidosis but have different noncardiac clinical features, such as maternally inherited diabetes, deafness, and recurrent strokes. Patients with advanced diabetes may have heavy proteinuria and heart failure, but their history of diabetes is obvious, and the echocardiogram does not show features suggestive of amyloid heart disease. In the era before echocardiography, constrictive pericarditis, often presenting with edema, ascites, and elevated jugular venous pressure with a Kussmaul sign, was the major differential of amyloid heart disease. Constrictive pericarditis is less common nowadays, and echocardiography can easily distinguish between the two entities.

■ AL AMYLOIDOSIS OF THE HEART

AL amyloidosis is a plasma cell disorder closely related to multiple myeloma. It is described in detail in [Chap. 117](#). An excessive production of abnormal lambda, or (less commonly) kappa, free light chains produced by abnormal clonal bone marrow plasma cells results in amyloid deposits in multiple organs, with heart and kidney being the most common organs involved. AL amyloidosis is closely related to multiple myeloma, with which it may occasionally overlap. It is an aggressive disease, and cardiac involvement, either alone or in combination with other major organ involvement, carries the worst survival, with a median survival from onset of heart failure to death in untreated patients of ~6 months. This short survival underscores the urgency of pursuing a diagnosis of AL amyloidosis once suspected, as therapy can markedly improve duration and quality of life and must be instituted as soon as the diagnosis is made. In addition to the general features of heart failure noted above, there are several clinical noncardiac clues to AL amyloidosis as the etiology of congestive heart failure. These indicate the presence of a multisystem disease and include significant proteinuria, neuropathy, periorbital purpura (virtually pathognomonic of AL amyloidosis and occurring in 20–30% of cases), and macroglossia (~10% of cases).

■ TTR AMYLOIDOSIS OF THE HEART

Patients with wild-type TTR amyloidosis cardiomyopathy and those with amyloid cardiomyopathy caused by variant TTR may have subtle differences in presentation. The less common variant TTR cardiomyopathy may be associated with amyloid neuropathy, which can vary between mild sensory neuropathy and a rapidly progressive severe sensorimotor neuropathy with or without autonomic nervous system involvement. Myocardial infiltration may be extensive in patients with severe variant transthyretin neuropathy, but cardiac symptoms can be relatively mild in these patients, either because the limitation of physical activity due to the neuropathy masks exercise intolerance or because autonomic neuropathy acts to reduce peripheral resistance, decreasing the work of the heart. If autonomic neuropathy is present, postural hypotension can be highly symptomatic and postural measurements of blood pressure are mandatory. A family history of neuropathy or cardiomyopathy may be elicited in these patients and, when neuropathy is present, may have been misdiagnosed as other neurologic conditions. In the United States, the most common TTR variant causing TTR amyloid cardiomyopathy is the substitution of valine for isoleucine at position 122, Val122Ile. This variant is present in ~3.5% of the U.S. population of African descent and presents as a late-onset restrictive cardiomyopathy usually in the seventh decade onward. The penetrance of clinical disease is incomplete, and the family history is often lacking or unknown. Neuropathy in this mutation is very mild or absent, although carpal tunnel syndrome, often preceding the onset of heart failure by several years, is commonly present. The clinical features of other forms of variant TTR amyloidosis can vary considerably, somewhat dependent on the transthyretin mutation, but in the case of the Val122Ile variant, it tends to be a relatively rapid progressive infiltrative cardiomyopathy with a median survival of 2–3 years following the onset of heart failure in untreated patients.

Once considered a rare form of cardiac amyloidosis, TTR deposition derived from native (wild-type) transthyretin is now considered the

most common form of amyloidosis. It affects mainly men in the latter half of their seventh decade and eighth decades but may occasionally present at a younger age and often presents in the ninth decade onward. Men are almost 20 times more likely than women to be diagnosed with wild-type TTR amyloidosis, and when it does occur in women, it tends to present at a later age and to have a more indolent course. On average, the untreated median survival from the onset of heart failure to death is around 4–5 years, with death being due primarily to progressive congestive heart failure rather than to sudden death. Current therapies have slowed the disease progression and improved survival. Both wild-type and mutant TTR cardiomyopathy have a subclinical phase, probably of several years, during which there is a progressive infiltration of the heart with amyloid, and by the time heart failure occurs, 30–50% of the involved heart weight is due to amyloid. Atrial arrhythmias, most commonly atrial fibrillation or atrial flutter, may be the presenting feature of the disease, and when they occur, they often precipitate or worsen heart failure. In contrast to AL amyloidosis, the heart in ATTRwt is the sole major organ to be clinically involved, although histologic examination of the lungs and gut often shows fairly extensive amyloid deposits. TTR also had a predilection for ligaments and tendons, and a history of carpal tunnel syndrome, spinal stenosis, or ruptured bicep tendon, often occurring 5–8 years before heart failure, can be elicited in about half the patients with this disorder.

■ DIAGNOSIS

The diagnosis of cardiac amyloidosis rests upon a clinical suspicion combined with imaging findings and, in many cases, a confirmatory biopsy. ECG voltage may be abnormally low, particularly in AL amyloidosis, but this is not always the case. Echocardiography is an extremely useful imaging modality. The echocardiogram in all forms of cardiac amyloidosis with heart failure shows increased left ventricular wall thickness without ventricular dilation and, frequently, biatrial enlargement ([Fig. 270-3](#)).

The right ventricle may also show increased thickness of the free wall. Diastolic function is abnormal, and a restrictive pattern, consistent with elevated left ventricular diastolic pressures, is often seen. Although the left ventricular ejection fraction may be normal or near-normal, left ventricular longitudinal strain imaging, a tool for measuring the contraction of the left ventricle in the longitudinal plane, often shows a pattern in which strain is relatively preserved at the left ventricular apex and severely impaired at the base of the heart. Color-coding of this pattern results in a “bull’s-eye” appearance, which is highly suggestive of cardiac amyloidosis ([Fig. 270-4](#)).

Atrial function is often impaired, particularly in AL amyloidosis, and this is characterized by a very small transmitral A wave in patients

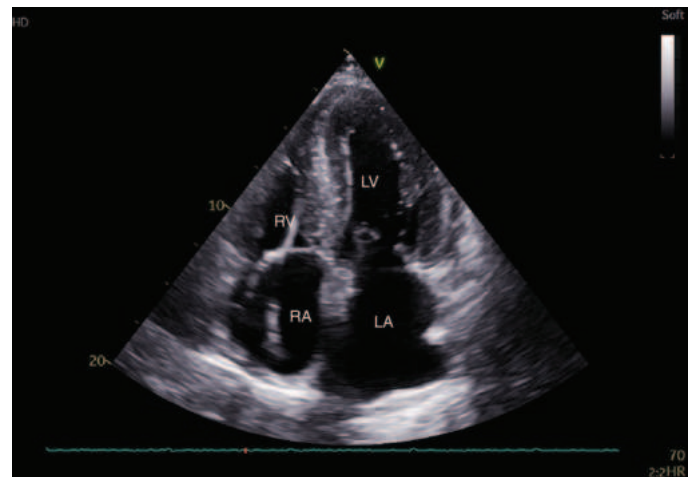


FIGURE 270-3 Echocardiogram (apical four-chamber view) showing typical appearance of amyloidosis. The left ventricular cavity is normal in size with thick walls, and there is biatrial enlargement. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

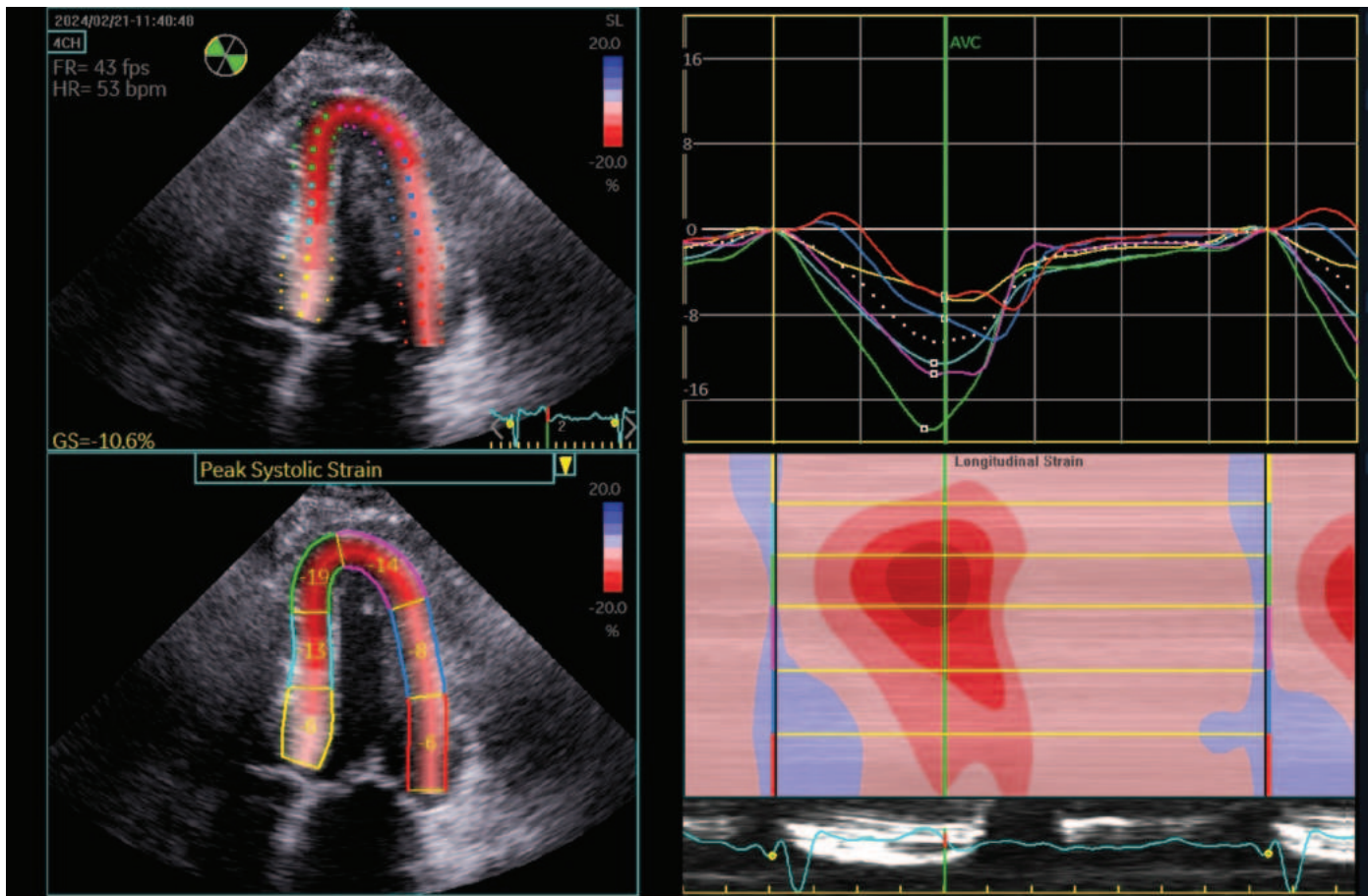


FIGURE 270-4 Left ventricular strain in amyloidosis. *Left panels* show outline of left ventricle divided into seven segments with numbers in bottom panel representing the percentage longitudinal systolic shortening of each segment. *Right top panel* shows corresponding curves for each segment, and *bottom right panel* shows color coding in which the apex codes bright red and base pink due to near-normal apical contraction, resulting in typical “bull’s-eye” pattern of amyloidosis.

in sinus rhythm. This appearance may be associated with an increased risk of thromboembolism.

Echocardiography with the typical appearance may be enough to proceed to further laboratory evaluation for amyloidosis, but cardiac magnetic resonance is increasingly used in the diagnosis of suspected cardiomyopathy. The ventricle is seen to be abnormally thick, measurement of extracellular volume demonstrates marked expansion of the extracellular space due to amyloid deposition, and there is often extensive delayed gadolinium enhancement of the myocardium, associated with abnormal nulling of the images (Figs. 270-5 and 270-6).

Taken together, these features are virtually pathognomonic of amyloid cardiomyopathy. Once amyloid cardiomyopathy is suspected, it is critical to determine the specific type of amyloid deposition. Tracers developed for bone imaging (technetium pyrophosphate or technetium 3,3-diphosphono-1,2-propanodicarboxylic acid [DPD]) are not usually taken up by the normal heart or in other forms of cardiac pathology, but there may be avid tracer uptake in patients with transthyretin amyloid cardiomyopathy (Fig. 270-7).

Because patients with AL amyloid cardiomyopathy may occasionally have myocardial uptake of these tracers, it is critically important to measure serum free light chains, serum and urine protein electrophoresis, and serum and urine immunofixation to rule out a plasma cell dyscrasia. If these lab tests are all negative and the nuclear scan is positive, a diagnosis of transthyretin amyloidosis can be confidently made, provided that echocardiography or cardiac magnetic resonance is consistent with this diagnosis. Monoclonal gammopathy of unknown significance not uncommonly coexists with transthyretin amyloidosis and will be associated with abnormalities in testing for plasma cell dyscrasia. Thus, if light chain amyloidosis remains a possibility, despite the presence of a strongly positive pyrophosphate scan, consultation with

a hematologist is important to help clarify the diagnosis. If uncertainty remains, an endomyocardial biopsy (or biopsy from other tissue) with definitive tissue typing (ideally by mass spectrometry) is required.

Almost all patients with light chain amyloidosis will have evidence of a plasma cell dyscrasia, and almost all of them will have elevation of either serum free lambda light chains or (less commonly) serum free kappa light chains. If light chain amyloidosis is clinically suspected and serum free light chains are elevated, it is mandatory to obtain a tissue biopsy to confirm the presence of amyloid deposits. Most patients with light chain amyloidosis have widespread systemic involvement, and a subcutaneous fat pad aspirate or deep skin biopsy will show amyloid deposits in the majority of cases, thus avoiding the necessity for a cardiac biopsy. If skin/fat biopsy is negative, it is reasonable to proceed to an endomyocardial biopsy. If amyloid heart disease is present, this will be positive in well over 90% of cases. In all cases, appropriate typing of the amyloid should be done to confirm the appropriate therapy. An algorithm with a suggested workup of suspected amyloidosis is shown in Fig. 270-8.

■ DIAGNOSIS AND TYPING OF CARDIAC AMYLOIDOSIS

Laboratory evaluation in patients with cardiac amyloidosis is generally nonspecific but may give some support to a suspected diagnosis. Electrolytes and complete blood count are usually normal or near normal. N-terminal prohormone of brain natriuretic peptide (NTproBNP) may be higher than anticipated for the degree of congestive heart failure, often in the range of 1000 to 2000 pg/mL even in the presence of relatively mild congestive heart failure. High-sensitivity troponin is frequently mildly elevated and may lead to a misdiagnosis of ischemic heart disease. In AL amyloidosis with renal involvement, heavy

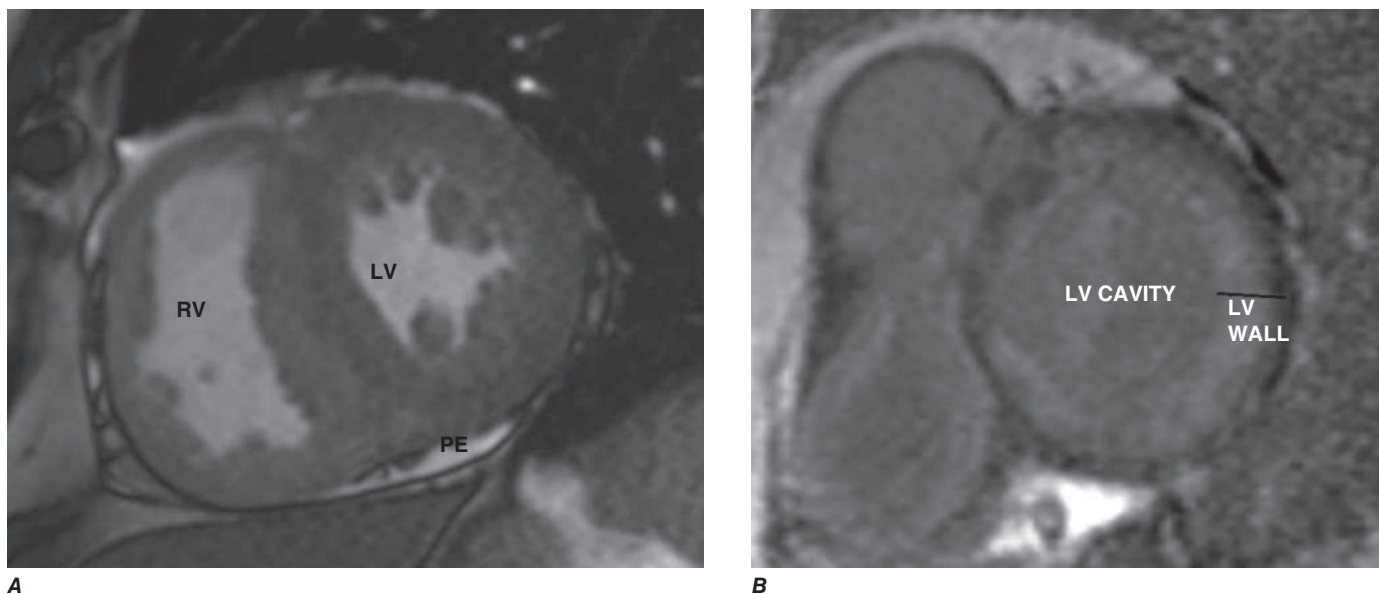


FIGURE 270-5 Typical cardiac magnetic resonance imaging (MRI) in amyloidosis. **A.** A typical cardiac MRI appearance in amyloid cardiomyopathy. The left ventricular (LV) cavity is small with a mildly dilated right ventricular (RV) cavity and thick LV walls. **B.** The appearance of late gadolinium enhancement after injection of gadolinium in the same patient. Two typical appearances are seen: the distinction between myocardium (*straight line*) and LV cavity is poor, due to delayed nulling of the myocardium, a near pathognomonic feature of cardiac amyloidosis. There is also extensive, transmural delayed gadolinium myocardial uptake due to severe amyloid infiltration. Another aspect of cardiac amyloidosis quantifiable by MRI (not shown) is measurement of extracellular volume, which is markedly increased in cardiac amyloidosis and helps to differentiate amyloid infiltration from true LV hypertrophy. PE, pericardial effusion. (Image courtesy of Dr. Sarah A. M. Cuddy, Brigham and Women's Hospital, Section of Cardiology.)

proteinuria is often found, and this may cause hypoalbuminemia. Renal involvement is not a feature of transthyretin amyloidosis. Rarely, in AL amyloidosis with hepatic involvement, the alkaline phosphatase is significantly elevated. Although AL amyloidosis is a plasma cell disorder closely related to multiple myeloma, the sedimentation rate is usually normal or only minimally elevated, unlike the marked elevation that may be seen in myeloma. Hypogammaglobulinemia may be present in AL amyloidosis, but serum and urine protein electrophoresis often do not reveal a monoclonal gammopathy, as the paraprotein level is low. Thus, in suspected AL amyloidosis, serum and urine immunofixation should be performed as these are more sensitive (although nonquantitative) than serum or urine protein electrophoresis. In almost all patients with AL amyloidosis, the level of circulating serum free light chains, either lambda or, less commonly,

kappa free light chains, is elevated. It is important to recognize that findings suggestive of a plasma cell dyscrasia in a patient with a cardiomyopathy needs to be interpreted in the context of the clinical picture, as monoclonal gammopathy of unknown significance is common in the older population and may be unrelated to the cardiomyopathy. Unlike TTR cardiomyopathy, there is no definitive noninvasive test to diagnose AL amyloid cardiomyopathy, and thus a tissue biopsy is always needed. A subcutaneous fat pad aspirate or deep-skin needle aspiration biopsy has a high yield of positivity, but needs to be evaluated by a skilled pathologist. A biopsy positive for AL amyloid from a noncardiac site in the presence of imaging consistent with amyloid cardiomyopathy is adequate to conclude that cardiac involvement is present. Immunohistochemistry, performed by many pathology labs, is fraught with diagnostic uncertainty and should be used with great

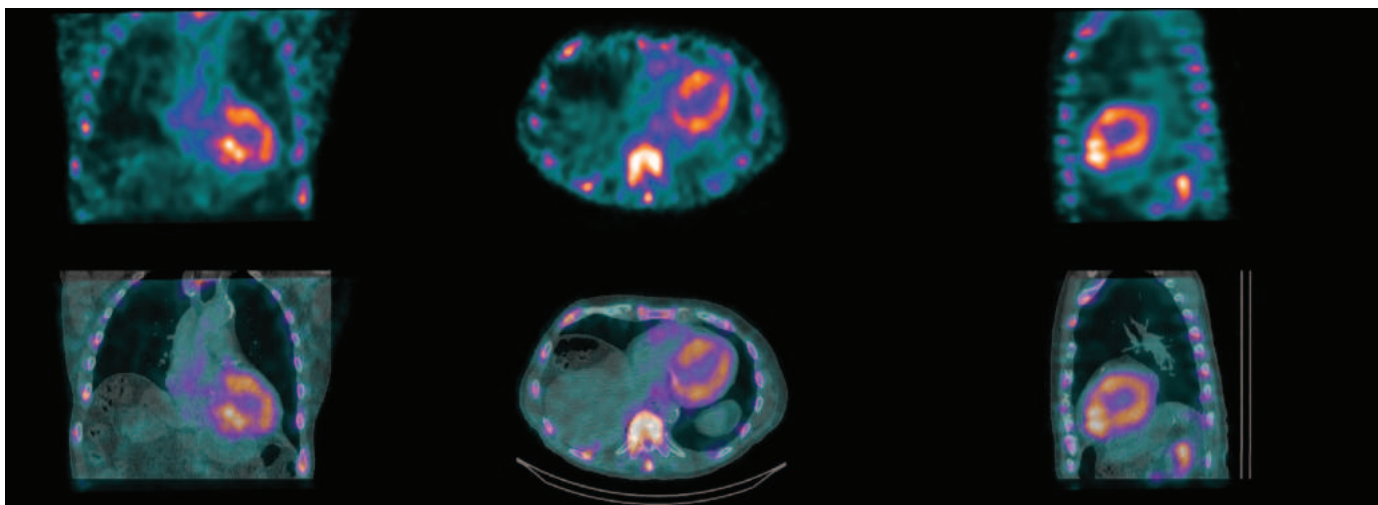
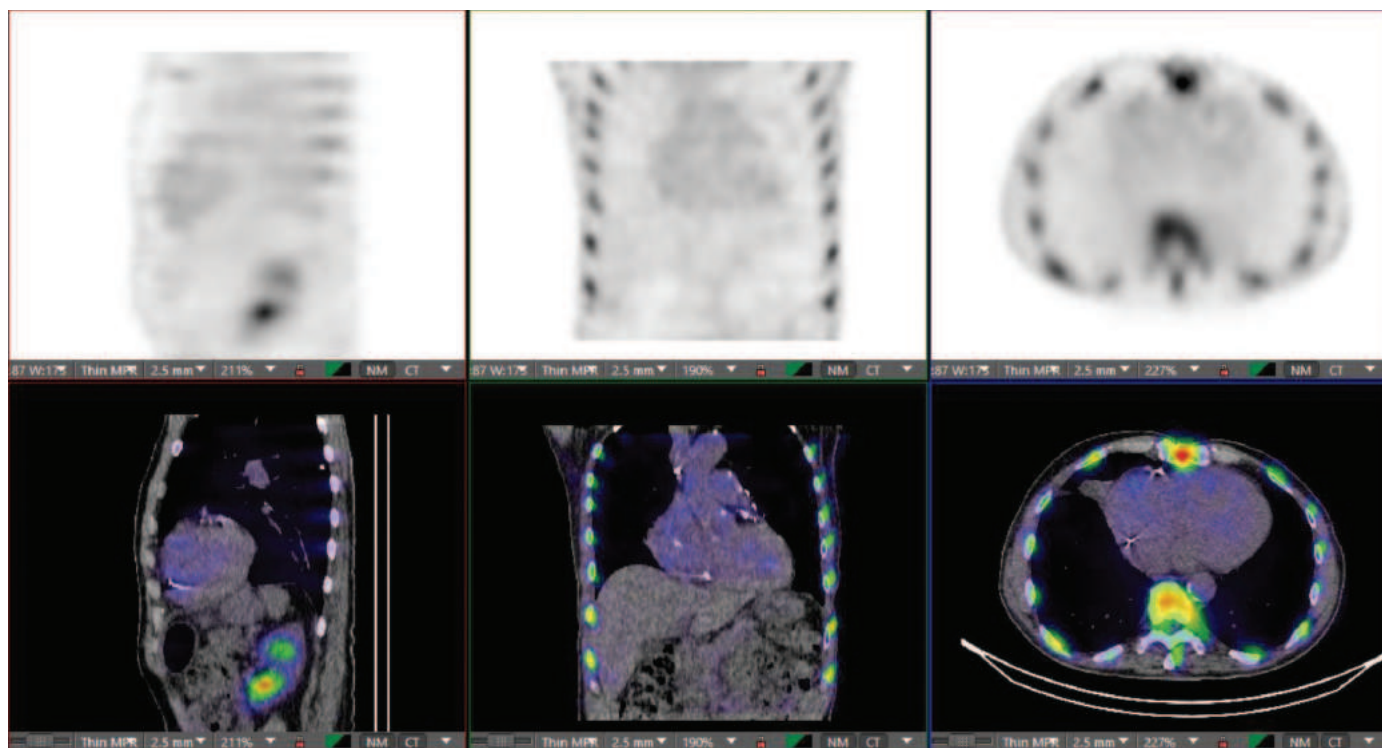
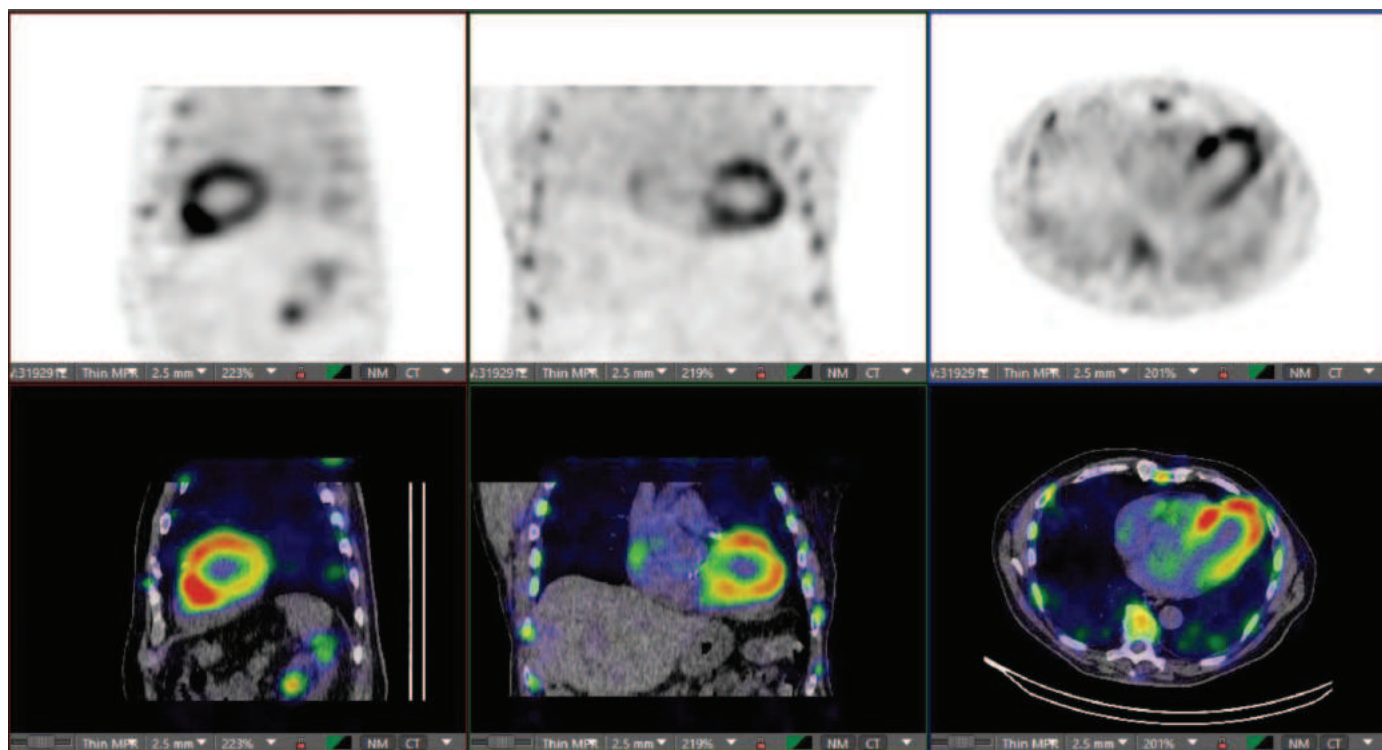


FIGURE 270-6 Technetium pyrophosphate (PYP) scan in a patient with wild-type transthyretin amyloidosis. The top three images are obtained in three separate views with single-photon emission computed tomography (SPECT) imaging alone, and the bottom three views with added cardiac CT imaging. Both modalities show marked myocardial uptake (*orange*) with absence of blood pool uptake (central clearing) and normal bone uptake. The lower images more precisely localize the uptake to the fused CT images of the heart, which in more equivocal cases helps to localize uptake to the myocardium and prevents misinterpretation as a positive scan due to blood pool uptake without myocardial uptake. PYP uptake is highly sensitive and specific for transthyretin amyloidosis but can occasionally be present in AL amyloidosis; thus, exclusion of a plasma cell dyscrasia is mandatory when interpreting this imaging. In the normal heart and almost all other pathologies, there is no myocardial uptake of bone tracers such as PYP.



A



B

FIGURE 270-7 Technetium pyrophosphate (PYP) scan. A. A normal (negative) PYP scan. The planar images (*top*) show rib and sternal isotope uptake, but there is no uptake in the heart. *Bottom* panel shows single-photon emission computed tomography–computed tomography (SPECT-CT) fusion showing normal appearance of nonamyloid heart after PYP imaging (no isotope uptake). **B.** Positive PYP scan in a patient with cardiac transthyretin amyloidosis. There is intense cardiac uptake on the planar imaging (*top*) which is confirmed to be in the wall of the heart on fused SPECT-CT images (*lower panel*). (Courtesy of Dr. Sharmila Dorbala, Brigham and Women's Hospital.)

caution and always interpreted in the setting of the clinical picture. It is thus strongly recommended that typing of the amyloid ideally be done by mass spectrometry (available as a “send-out test” in the United States). Unless a diagnosis of AL amyloidosis is clear, sequencing of the TTR gene should be done to rule out familial transthyretin amyloidosis as this has obvious ramifications for the family.

TREATMENT

Cardiac Amyloidosis

The treatment of systemic amyloidosis is addressed in detail in [Chap. 117](#). Here, we will concentrate on specific issues related to

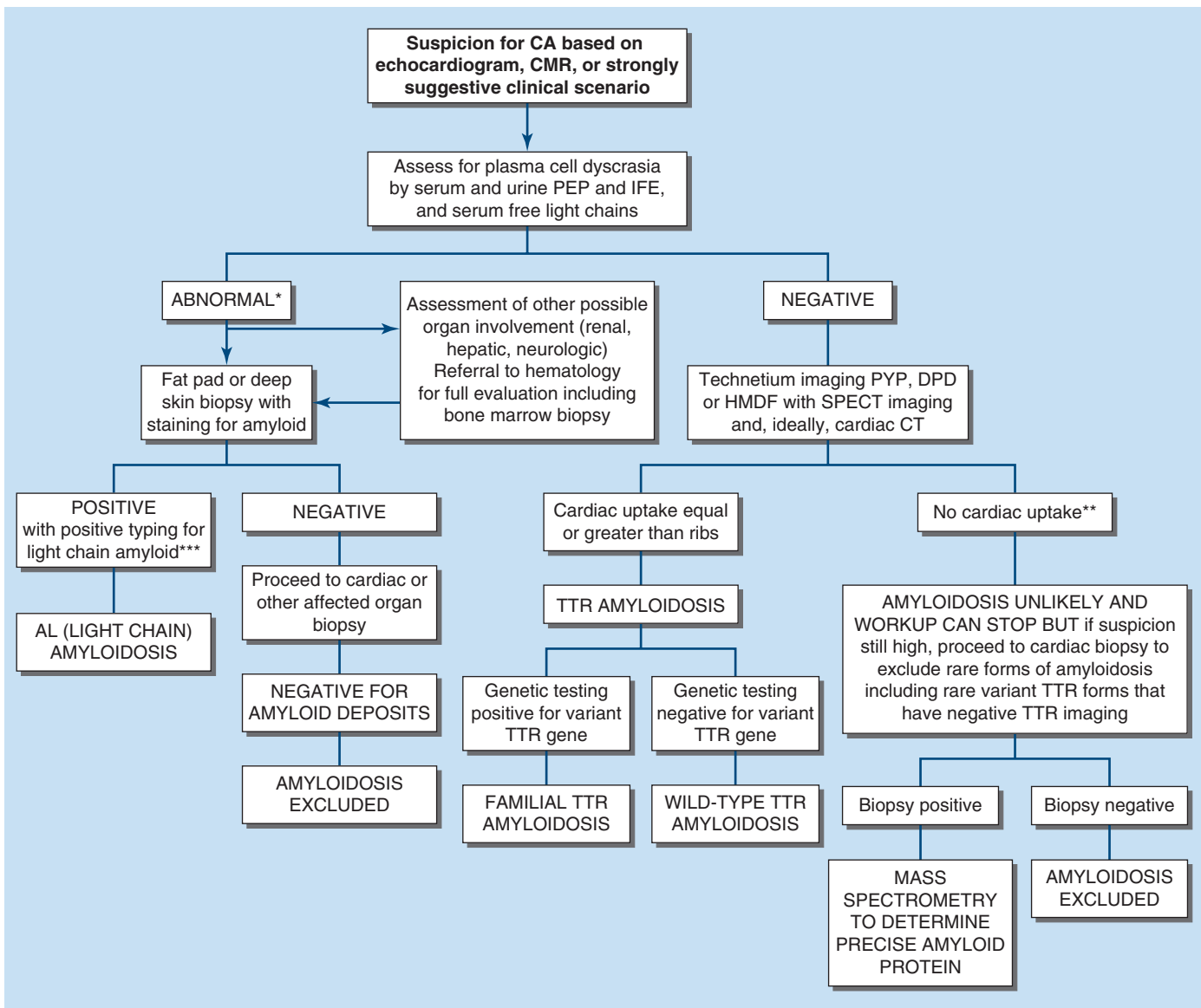


FIGURE 270-8 Diagnostic algorithm. Algorithm for the workup of suspected cardiac amyloidosis (CA). This is a suggested algorithm but, depending on initial degree of suspicion for amyloidosis type, may vary slightly in order. Asterisk footnotes are as follows: *Normal values in workup for a plasma cell dyscrasia are negative serum and urine protein electrophoresis and immunofixation, with normal values for free serum kappa and lambda light chains adjusted for renal function. Abnormalities may not always reflect light chain amyloidosis, as monoclonal gammopathy of unknown significance not uncommonly coexists with TTR amyloidosis and thus expert evaluation of all abnormalities is mandatory. **Patients with bone-imaging uptake present but less than rib uptake should be carefully evaluated to ensure that this is not just blood pool isotope uptake and, if not, should be considered as possible amyloidosis with further evaluation based on expert evaluation of likely cardiac amyloid. ***Typing for amyloidosis should ideally be performed by mass spectrometry, generally only available in specialized centers. Immunohistochemistry, while often used, may be misleading and should be interpreted cautiously within the context of the clinical features of the disease. CMR, cardiac magnetic resonance; CT computed tomography; DPD, technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid; HMDP, technetium-99m-hydroxymethylene diphosphonate; IFE, immunofixation electrophoresis; PYP, technetium-99m-pyrophosphate; PEP, protein electrophoresis; SPECT, single-photon emission computed tomography.

the cardiac disease. It is important, when considering treatment of cardiac amyloidosis, not simply to focus on therapies aimed at slowing or stopping the production of the precursor protein but also to address the manifestations of the disease. Sodium restriction is an integral part of management of heart failure in all forms of cardiac amyloidosis with congestive heart failure. The restrictive pathophysiology renders the patient particularly vulnerable to small changes in blood volume, and sodium restriction can significantly improve the response to diuretics. There are no specific clinical trials that evaluate the best way to treat congestive heart failure in cardiac amyloidosis, but it is generally recognized that diuretics are the mainstay of therapy. The combination of a loop diuretics such as furosemide or (preferably) torsemide with spironolactone or eplerenone is usually well tolerated. Renal function should be monitored while adjusting diuretic dose, particularly in patients with ATTRw amyloidosis who tend to be older and to have more baseline renal impairment. The use of other drugs commonly used in congestive

heart failure is more controversial. In light chain amyloidosis, autonomic function is often impaired even in the absence of postural hypotension, and the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be associated with profound hypotension. Thus, they are generally avoided. Beta-blockade is also often problematic and associated with decreased exercise tolerance. If a patient is receiving beta blockers when initially seen, we routinely taper and stop their use and reassess the patient's sense of well-being, which, not infrequently, improves. For patients with atrial fibrillation and a rapid ventricular response, beta-blockade may be needed but digoxin can also be used. However, restoration of sinus rhythm is preferable. The use of sodium-glucose cotransporter 2 (SGLT2) inhibitors appears to be clinically well-tolerated. This class of drug has efficacy across the spectrum of patients with heart failure and preserved ejection fraction and those with heart failure and reduced ejection fraction and may be of value in cardiac amyloidosis.

Cardiac arrhythmias in both AL and TTR amyloidosis are common. Most frequently seen is atrial fibrillation or flutter, the onset of which is often associated with clinical deterioration. There is a high risk of thromboembolism in patients with cardiac amyloidosis, and anticoagulation in patients with atrial fibrillation or flutter is mandatory. There does not appear to be increased risk of major bleeding among patients taking anticoagulants in either light chain or transthyretin amyloidosis. Restoration of sinus rhythm should be considered in all patients, particularly since rate-controlling agents are poorly tolerated. Amiodarone appears to be the most effective antiarrhythmic drug for atrial arrhythmias and should ideally be given, starting with a loading dose, prior to elective electrical cardioversion. If a patient is adequately anticoagulated before and during electrical cardioversion, there is no reason to perform transesophageal echocardiography prior to the procedure. If atrial arrhythmias are associated with clinical deterioration and sinus rhythm cannot be maintained despite antiarrhythmic therapy, consideration should be given to an invasive electrophysiologic procedure. Pulmonary venous isolation/atrial fibrillation ablation is often more complex than in nonamyloid patients, with a higher recurrence rate, and we therefore tend to limit ablation procedures to patients with atrial flutter and no evidence of atrial fibrillation. For those with symptomatic atrial fibrillation, atrioventricular nodal ablation with the implantation of a biventricular pacemaker is an effective way of both controlling and regularizing the ventricular rate. Sudden cardiac death may occur in cardiac amyloidosis, being more common in advanced AL amyloidosis, but a prophylactic implantable defibrillator is generally ineffective in preventing this. Thus, consideration of an implantable defibrillator should be highly selective and probably limited to patients with a prior resuscitated cardiac arrest or a history of sustained ventricular tachycardia.

Patients with TTR amyloidosis are at a high risk for the development of high-degree atrioventricular block. This is usually preceded on ECG by bifascicular block or left bundle branch block. Patients should be questioned about unexplained, nonpostural dizzy spells or syncope, and if these occur in the setting of one of these ECG abnormalities, strong consideration should be given to cardiac pacing. If a pacemaker is to be placed, we would generally recommend biventricular pacing, as right ventricular pacing produces abnormalities of septal contraction that, in the presence of a small cavity ventricle, may decrease cardiac output.

SPECIFIC THERAPY OF CARDIAC AMYLOIDOSIS: AL AMYLOIDOSIS

The most common regimen for treating patients with light chain amyloidosis includes daratumumab, bortezomib, cyclophosphamide, and dexamethasone. Dexamethasone may aggravate sodium retention, and it is critical that the cardiologist experienced in

amyloidosis co-manages AL amyloidosis patients with cardiac involvement along with the treating hematologist. During therapy, an increased diuretic dose may be needed and/or a reduction in the dexamethasone dose. The other medications are generally well tolerated, but rarely, bortezomib may cause acute, reversible cardiac toxicity. Bortezomib may also cause a neuropathy and aggravate autonomic neuropathy of AL amyloidosis. High-dose melphalan chemotherapy with autologous stem cell transplantation is used in some patients with light chain amyloidosis and may be associated with considerable fluid retention or atrial arrhythmias in patients with cardiac involvement. For patients with AL cardiac amyloidosis, it is mandatory that the patient being considered for this therapy have a pretherapy cardiac evaluation to assess the risk-benefit ratio, along with regular posttransplant follow-up in the acute stage. Following successful chemotherapy (defined as a hematologic remission, with normalization of the serum free light chains), congestive heart failure often improves and is associated with an improvement in left ventricular longitudinal strain. However, some patients remain with very poor cardiac function. Such patients may benefit from cardiac transplantation, but this requires a very careful evaluation at an expert center to determine the extent of extracardiac amyloidosis and its likely effect on posttransplant prognosis.

SPECIFIC THERAPY OF CARDIAC AMYLOIDOSIS: TTR AMYLOIDOSIS

Currently, the aim of treatment of TTR cardiac amyloidosis is focused on reducing or stopping any further amyloid deposition. Tafamidis, a small molecule that stabilizes the tetrameric structure of transthyretin, is effective at slowing disease progression and may halt progression among patients treated early in the clinical presentation of the disease. It is extremely well tolerated. A similar drug, acoramidis, has shown similar efficacy in a pivotal clinical trial. An alternative class of drugs, the TTR silencers, significantly reduce the production of transthyretin by the liver and are approved in the United States for the treatment of familial amyloid polyneuropathy. At the time of writing, two drugs (both of which are only approved for amyloid neuropathy), eplontersen and vutrisiran, both administered subcutaneously, are completing clinical trials for the treatment of transthyretin amyloid cardiomyopathy.

Rarer forms of cardiac amyloidosis are listed in [Table 270-2](#). Their rarity relates to the very uncommon nature of the type of amyloid with which they are associated or, as in the example of AA amyloidosis, the uncommon nature of cardiac involvement despite extensive other involvement. The diagnosis of most of these forms of cardiac amyloidosis will be made on mass spectrometry of a tissue biopsy after cardiac amyloidosis is suspected but when there is no evidence of a plasma cell dyscrasia or abnormality on technetium imaging.

TABLE 270-2 Rare Forms of Amyloidosis

AMYLOID TYPE	PRECURSOR PROTEIN	FREQUENCY OF CARDIAC DISEASE	OTHER ORGAN INVOLVEMENT	COMMENT
AA	Serum amyloid A (an inflammatory protein)	<5%	Kidney, liver	Usually associated with longstanding chronic inflammation. Uncommon in developed countries, and cardiac involvement rarely the predominant factor.
AApoA1	Apolipoprotein 1	25–30%	Kidney, liver, spleen, nervous system, larynx	Rare condition, with family history in many cases. Cardiac disease, when present, may be predominantly right-sided with tricuspid valve involvement.
AapoA4	Apolipoprotein 4	65–70%	Kidney	Family history often not present. Renal involvement without proteinuria is common, and cardiac involvement is usually present but often relatively mild.
Afib	Fibrinogen A-alpha (gene mutation)	Not described	Kidney, spleen	Rare. Proteinuria that progresses to renal failure. Typical renal biopsy with glomerular obliteration by amyloid. Typical amyloid cardiomyopathy absent.
ALECT2	Leukocyte cell-derived chemotaxin 2	Not described	Kidney	Liver involvement common. ALECT2 predominantly found in Hispanics.
Gelsolin	Gelsolin	Unknown prevalence. Usually mild, and manifesting as conduction disease	Corneal lattice dystrophy Skin and neurologic features	Predominantly found in Finnish patients.

SUMMARY

Over the past several years, cardiac amyloidosis has come to be recognized as a much more common disease than previously appreciated. In part, this is due to the aging population, in whom TTR amyloidosis is a significant cause of heart failure. The ability to diagnose TTR amyloidosis with noninvasive nuclear scanning rather than needing cardiac biopsy has made the diagnosis much easier, and the availability of effective disease-modifying treatment has added an incentive to diagnose previously untreated disease. AL amyloidosis, although more complex to diagnose, is seen in younger patients, and now effective life-saving treatments and therapies for both types of cardiac amyloidosis are expanding. While a high degree of suspicion is needed to diagnose these diseases, the benefits of diagnosis to the patient are considerable, and the satisfaction of being able to treat a previously untreatable condition is one of the most gratifying aspects of the practice of medicine.

FURTHER READING

DORBALA S et al: How to image cardiac amyloidosis: A practical approach. *JACC Cardiovasc Imaging* 13:1368, 2020.

IOANNOU A et al: Rare forms of cardiac amyloidosis: Diagnostic clues and phenotype in Apo AI and AIV amyloidosis. *Circ Cardiovasc Imaging* 16:523, 2023.

KITTLESON MM et al: 2023 ACC Expert Consensus Decision Pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: A report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 81:1076, 2023.

RUBERG FL, MAURER MS: Cardiac amyloidosis due to transthyretin protein: A review. *JAMA* 331:778, 2024.

WECHALEKAR AD et al: AL amyloidosis for cardiologists: Awareness, diagnosis, and future prospects: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol* 4:427, 2022.

271

Cardiac Transplantation and Prolonged Assisted Circulation

Mandeep R. Mehra



Advanced heart failure, a distinct syndrome, is characterized by refractoriness to conventional therapy and represents a clinical dilemma associated with an increased symptom burden, frequent hospitalization, a poor quality of life, and high risk of death. Such individuals do not tolerate neurohormonal antagonists at recommended doses, exhibit worsening renal function, maintain poor cardiac reserve on cardiopulmonary stress testing, and typically display a low cardiac output state with elevated pulmonary pressures on invasive hemodynamic assessment. In general, therapeutic targets shift away from disease-modifying or neurohormonal therapy to surgical options that attend directly to supporting the dysfunctional heart and address myocardial stress and strain relationships. Most often, prolonged circulatory assistance using mechanical ventricular assist devices or cardiac transplantation is required to reliably improve quality of life and long-term survival.

CARDIAC TRANSPLANTATION

A decade after Norman Shumway had accomplished the technique of a successful heart transplant in canines, Christiaan Barnard successfully performed the first human-to-human transplant on December 3, 1967. Now, >5 decades later, this surgery has become entrenched in the standard armamentarium for treating patients with advanced heart failure who are otherwise healthy enough to receive such a life-altering

treatment. Globally, >150,000 patients have undergone cardiac transplantation with a 1-year survival >80% and median survival of 12.5 years and conditional survival of 14.8 years if the recipient survives the first year after transplant. These gains have been ushered in by advances in immunosuppression, identification and management of allograft rejection, and a comprehensive appreciation for late complications including accelerated coronary artery disease, malignancy, and renal failure.

CANDIDATES FOR CARDIAC TRANSPLANTATION

The demand for cardiac transplantation outstrips the availability of organ donors. Hence, attention to the optimal utility, equitable allocation, and patient autonomy must dominate decisions to identify and list candidates for transplantation. Simultaneously, attempts at expanding the donor pool have surfaced. However, vigilance to evaluating candidates most likely to have a successful outcome from transplantation takes pre-eminence. In 2006, the International Society for Heart and Lung Transplantation identified a set of criteria to guide listing of patients. These criteria were updated in 2016 and include additional attention to the growing epidemiology of candidates suffering from congenital heart disease, restrictive and infiltrative cardiomyopathy (such as amyloidosis), and chronic infections in recipients (such as Chagas’ disease, tuberculosis, and viral hepatitis). Selected general principles for listing candidates for cardiac transplantation are enumerated in [Table 271-1](#).

PRINCIPLES OF DONOR RECOVERY AND ALLOCATION

Although listing criteria for candidates are typically adjudicated at an individual center level, organ allocation is handled by national regulatory processes in most countries. The allocation of donor hearts is based on (1) the urgency of the recipient clinical situation, (2) the length of time spent on the waiting list, (3) the distance from the recipient center, and (4) blood group. Candidates who are hospitalized in critical status and require extracorporeal membrane oxygenation

TABLE 271-1 Principles for Listing Candidates for Cardiac Transplantation	
PRINCIPLE	COMMENT
Advanced disease severity	Refractory heart failure with a VO_2 of <14 mL/kg per min (<12, if on beta blockers) or percent predicted VO_2 <50%; combination of intolerance to disease-modifying therapy, cardiorenal syndrome, use of inotropic therapy to maintain stability, or need for a left ventricular assist system.
Comorbidity	Age is not an absolute contraindication, but frailty should be considered a relative contraindication; a BMI >35 kg/m ² should require weight loss; cancer should be dealt with on an individual basis (e.g., low-grade prostate cancer may not be a contraindication); poorly controlled diabetes mellitus or end-organ damage may be a contraindication; eGFR <30 mL/min/1.73 m ² is a relative contraindication (and requires consideration for a combined kidney transplant), if persistent; severe cerebrovascular disease or peripheral vascular disease (which will limit rehabilitation or function) is also a relative contraindication.
Donor-recipient matching	Sensitized individuals with circulating antibodies should have a prospective or virtual cross match; pulmonary vascular resistance with a transpulmonary gradient >15, PVR >3 Wood units, and absolute PA systolic pressure >50 mmHg (provided the systolic blood pressure is >85 mmHg) is a relative contraindication unless reactive to therapy.
Psychosocial issues	Tobacco use in any form limits posttransplant survival and should be stopped for at least 6 months; substance abuse, including marijuana, should be a contraindication if the individual cannot demonstrate control and cessation; patients with severe cognitive-behavioral disabilities or dementia (inability to ever understand and cooperate with medical care) have the potential for self-harm and should not receive a transplant.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; PA, pulmonary artery; PVR, pulmonary vascular resistance; VO_2 , peak oxygen consumption.

or temporary mechanical circulatory support devices to support both ventricles are given the highest urgency status, followed by those requiring daily invasive hemodynamic evaluation and intravenous inotropic therapy to maintain stability, or those with complications of a durable left ventricular assist device. Others stable at home while supported by a left ventricular assist device or those able to ambulate and live at home receive a lower urgency status. The geographical regional reach for allocation is based not only on territorial considerations but also on the time that a donor heart would be in transit and therefore in out of body “ischemia time,” which is typically limited to 4 h, unless novel techniques for organ transport are employed. A key feature that is included in the allocation offer relates to the ABO blood group as well as the size match of a potential donor with the recipient. Donor organs are offered based on these initial characteristics and then a more detailed donor assessment ensues, resulting in acceptance or decline for any given donor heart. It is important to note that the time constraints imposed on the retrieval process make it difficult to invoke HLA matching of the donor and recipient. In cases where there is a high likelihood of allosensitization in the recipient (preformed circulating antibodies against donor antigens), a prospective or virtual cross match is entertained prior to acceptance. Other clinical criteria that are employed in the decision on accepting an offered donor include the donor-recipient size match (donor body weight no greater than 30% below that of the recipient if it is a same sex transplant, or no greater than 20% for a female to male transplant or assessed using a predicted heart mass calculator), the age of the donor (typically restricted to <55 years, but is often exceeded due to organ shortages), and presence or absence of concomitant pathology such as coronary artery disease, left ventricular hypertrophy, or severe injury to the allograft manifest by excess leak of injury markers (troponins) or poor contractile performance that does not improve in serial testing. In many cases, the prospective cardiac allograft can be reconditioned over time and used for transplantation even if the initial evaluation suggests poor contractile function. In efforts to enhance the donor pool, systems that allow ex situ normothermic perfusion to evaluate and reanimate organs with a prolonged out of body time have been developed that allow use of organs that may otherwise have been discarded. The classical heart donor is derived from a donor with established brain death; however, donors after circulatory death are being increasingly evaluated as candidates for cardiac reanimation using a variety of techniques including ex situ reanimation and subsequent transplantation. Such donor organs obtained after circulatory death are gaining widespread acceptance, and studies suggest that their outcomes after transplantation are no different from those of organs retrieved from brain death donors. However, this donor source is subject to ethical controversy in some

geographical regions of the world. To increase the number of viable donors, organs from those infected with hepatitis C virus are increasingly being utilized since preventive or curative antiviral therapy can be used in the recipient shortly after transplantation.

■ SURGERY FOR CARDIAC TRANSPLANTATION

The most common contemporary operation is referred to as a “bicaval” orthotopic cardiac transplant that mimics the natural anatomic position. In this operation, the donor and recipient superior and inferior venae cavae are connected as are the aortic and pulmonary great vessels. The left atrium of the recipient retains its roof including the draining pulmonary veins, and the donor left atrium is then sutured to the retained atrial tissue. This technique maintains function of the donor right atrium, important for governing early postoperative right heart output, and may prevent atrial arrhythmias. The recipient is left with a surgical denervation, and the allograft is not responsive to any physiologic sympathetic or parasympathetic stimuli. Therefore, early in the adaptive postoperative phase, high-dose catecholamines are required to maintain adequate function. Due to denervation, bradycardia in a cardiac allograft cannot be treated with atropine and the drug of choice is isoproterenol, or temporary electrical pacing is used. Once the cardiac allograft adapts to its host circulation, the function is usually adequate at rest and with exercise, to provide normal physical activity and quality of life.

■ CARDIAC ALLOGRAFT REJECTION AND IMMUNOSUPPRESSION

The ability to perform endomyocardial biopsies and evaluate rejection pathologically and the introduction of the immunosuppression agent cyclosporine heralded cardiac transplantation as a viable clinical therapy. Triple-drug immunosuppression, which includes a calcineurin inhibitor (cyclosporine or tacrolimus), corticosteroids, and antiproliferative immunosuppression (azathioprine, mycophenolate mofetil, sirolimus, or everolimus), is now the standard combination used. The combination immunosuppression strategy that is most used and that achieves the best standard outcomes includes tacrolimus, mycophenolate mofetil, and prednisone. In those at high risk for rejection (multiparous women, allosensitized individuals, retransplants) or in situations where use of calcineurin inhibitors needs to be delayed (renal dysfunction), induction therapy using monoclonal (basiliximab) or polyclonal antibodies (antithymocyte globulin) to provide augmented immunosuppression is used, although this strategy remains poorly studied. Over several months, as surveillance endomyocardial biopsies are regularly performed and clinical as well as subclinical pathologic quiescence is established, gradual weaning of steroids is undertaken, in some cases to the point of elimination. **Table 271-2** describes the immunosuppression drugs in common use.

TABLE 271-2 Immunoprophylaxis Drugs in Cardiac Transplantation

DRUG CLASS	GENERIC DRUG	CELLULAR TARGET	MAJOR SIDE EFFECTS
Calcineurin inhibitors	Cyclosporine	Binds to cyclophilin, which then inhibits calcineurin	Hypertension, dyslipidemia, gum hypertrophy, hypertrichosis
	Tacrolimus	Binds to immunophilin FK506 binding protein, which inhibits calcineurin	Hypertension, dyslipidemia, alopecia, diabetes mellitus
Antithymocyte globulin (ATG)	Rabbit ATG	T-cell depletion in blood and peripheral lymphoid tissues through complement-dependent lysis and T-cell activation and apoptosis	Cytokine release syndrome, leukopenia, thrombocytopenia, serum sickness
	Horse ATG	Same as above	Same as above
Interleukin-2 receptor antagonists	Basiliximab	Inhibition of CD-25 of interleukin 2 receptor	Well tolerated; rare hypersensitivity; increased infection risk if used with calcineurin inhibitors
Antimetabolites	Azathioprine	Imidazolyl derivative and prodrug of 6-mercaptopurine (cell cycle inhibitor)	Bone marrow suppression, pancreatitis, hepatitis
	Mycophenolate Mofetil	Inhibits inosine monophosphate dehydrogenase, which controls guanine monophosphate in the de novo pathway of purine synthesis (inhibits T- and B-cell proliferation)	Leukopenia, gastrointestinal toxicity
Proliferation signal inhibitors	Sirolimus	Binds with FKBP12 and complex inhibits the mechanistic target of rapamycin (mTOR)	Delayed wound healing, nonspecific pneumonia, pericardial effusion, hyperlipidemia (hypertriglyceridemia)
	Everolimus	Binds to FKBP12, which inhibits mTORC1 (and not mTORC2)	Dyslipidemia, stomatitis, pericardial effusions, and pancytopenia

Acute cellular rejection (ACR) and antibody-mediated rejection (AMR) are two separate forms of cardiac allograft rejection that are recognized and can sometimes coexist. ACR occurs early after transplantation and then tends to decline in incidence after 6 months. This occurs due to a T cell-mediated assault on the donor allograft tissue and histologically is characterized by lymphocytic infiltrates in the myocardium. In mild cases, these infiltrates are localized to the perivascular regions, and in severe cases, they progress diffusely into the cardiac interstitium. In late stages of severe ACR, most often associated with hemodynamic compromise, multiclonal cells such as macrophages, neutrophils, and eosinophils are observed with intramyocardial hemorrhage, myocyte injury, and myocyte necrosis. Subclinical ACR is typically treated with high doses of corticosteroid pulses, although some centers choose to simply observe mild forms of infiltration since it is known that many of these patients may recover spontaneously over time. If hemodynamic compromise occurs, rescue polyclonal antibodies are used in tandem with corticosteroids. Conversely, AMR is immunologically described as a noncellular antibody-driven phenomenon associated with a pattern of immunopathologic findings of immunoglobulin deposition and complement fixation on immunofluorescence, along with histopathologic findings of endothelial swelling and interstitial edema and cardiac allograft arteriolar vasculitis. AMR is characterized by the emergence of circulating donor-specific antibodies that are thought to fix complement and bind to the allograft. Commonly, AMR leads to allograft dysfunction, increases the risk for development of cardiac allograft vasculopathy, and is associated with worsened cardiac allograft survival compared with ACR. In this form of rejection, therapy is directed toward suppression and removal of circulating antibodies using plasmapheresis and drugs such as rituximab (chimeric monoclonal antibody directed against the CD20 antigen) or, in refractory cases, bortezomib (a proteasome inhibitor) or eculizumab (a terminal complement inhibitor). Intravenous immunoglobulin is also used as an immune-modulatory agent. The treatment with immunosuppression requires prophylaxis for opportunistic infections and ongoing surveillance and expertise in recognizing the more common clinical presentations of infections caused by cytomegalovirus (CMV), *Aspergillus*, and other opportunistic agents such as *Nocardia* and toxoplasmosis.

■ LATE COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

The long-term consequences of exposure to chronic immunosuppression result in a variety of nonimmunologic cardiometabolic effects such as hypertension, hyperlipidemia, and hyperglycemia, as well as systemic disorders of bone loss and renal dysfunction. One aggressive complication that limits late survival of cardiac allografts includes the development of an accelerated form of coronary artery disease, referred to as cardiac allograft vasculopathy (CAV). This is characterized by a proliferative thickening of the vascular intima of the vasculature that is initiated as a diffuse endothelialitis in the setting of the confluence of the consequences of brain death, ischemia reperfusion injury during the transplant process, and early immunologic insults. Chronically, the metabolic consequences of hypertension, hyperlipidemia, and disordered glucose regulation result in worsening of vascular lesions that are diffuse and noted throughout the coronary tree. Early diagnosis and preventative therapy are critical since it is commonly silent in its development. Intravascular ultrasound or optical coherence tomography is more sensitive than routine coronary angiography for the diagnosis of CAV. A standardized grading scheme for CAV was proposed by the International Society for Heart and Lung Transplantation in 2010. CAV is graded as absent (CAV0), mild (CAV1), moderate (CAV2), or severe (CAV3) based on extent of angiographic disease and presence of allograft dysfunction by echocardiography or restrictive cardiac physiology. The grade of CAV correlates with patient prognosis. Angiographic CAV is present in ~30% of patients by 5 years after transplant and ~50% of patients by 10 years after transplant. Use of noninvasive testing for coronary flow reserve has been demonstrated to arbitrate prognosis in CAV. Use of statins may help prevent CAV development after heart transplantation, and targeting lipid lowering using

nonstatin drugs (e.g., PCSK9 inhibitors) has shown promise. Anti-hypertensive agents and anti-CMV therapy have demonstrated some benefits in reducing CAV with varying degrees of supportive evidence. Antiproliferative immunosuppressive therapy such as mycophenolate mofetil and sirolimus or everolimus prevents vascular intimal thickening compared with azathioprine-based regimens. Use of the chimeric monoclonal antibody directed against the CD20 antigen, rituximab, may accelerate CAV. Options for medical treatment of established CAV remain limited. Revascularization using percutaneous coronary intervention or coronary artery bypass grafting may be employed in selected cases with focal lesions but does not improve survival in patients with CAV. However, retransplantation is the only definitive form of therapy for advanced CAV (Fig. 271-1).

Another concern in cardiac transplantation is the development of malignancy with a greater frequency than in the normal population, suggesting that immunosuppression plays a sentinel role in its generation. Posttransplant lymphoproliferative disorders, typically driven by Epstein-Barr virus, occur most frequently and require a reduction in immunosuppression, administration of targeted antiviral agents, and traditional chemo- and radiotherapy. Specific antilymphocyte (targeted against CD20) therapy has also shown promise. Solid cancers most often manifest as skin malignancies (both basal cell and squamous cell carcinomas), and regular use of sunscreen is advised. Future research is required to define strategies for immune modulation, immune suppression, and malignancy prevention; however, the impact of decreasing immunosuppression in the treatment of these cancers remains unclear.

PROLONGED ASSISTED CIRCULATION

The quest for a prolonged and durable implantable mechanical circulatory support device has led to the development of continuous flow left ventricular assist systems (LVAS). Initially designed for short-term support as a bridge to recovery or to cardiac transplantation, the most frequent use today entails permanent support for lifetime therapy ("destination therapy"). The decision to implant LVAS dichotomously as either a bridge to transplantation or for destination therapy is not always clear, and in several instances, these devices are used as a "bridge to decision" (in those with potentially reversible underlying relative contraindications such as renal insufficiency or pulmonary hypertension, who may become future candidates for transplantation).

■ LEFT VENTRICULAR ASSIST SYSTEMS AND CLINICAL TRIALS

A pivotal trial, REMATCH, published in 2001, was the first study to reliably demonstrate that survival of patients with transplant-ineligible, refractory, predominantly inotropic therapy-supported heart failure is improved by implantation of an LVAS. This study used an early-generation pulsatile flow device and demonstrated a 48% reduction in risk of death. However, the LVAS used was of limited durability, and meaningful "out of hospital" survival was prolonged by a median of only 5 months. Furthermore, complications of strokes, multisystem organ failure, and infections reduced enthusiasm for widespread adoption. Over time, continuous flow systems that had small turbo-pumps with minimal moving parts and no valves were introduced, leading to greater durability and more generalized worldwide adoption.

A landmark trial compared the older bulky pulsatile LVAS studied in the REMATCH trial with a newer generation axial continuous flow LVAS, the HeartMate II, and demonstrated a marked improvement in short- and long-term survival, along with an improvement in functional capacity and meaningful quality-of-life enhancement. A centrifugal continuous flow LVAS, the HeartWare HVAD, was also introduced and demonstrated noninferiority to the HeartMate II pump. The HeartMate II is no longer used, and the HVAD has been removed from global distribution. A newer centrifugal device with a fully magnetically levitated system, the HeartMate 3 LVAS, is now the most used pump due to demonstration of reduced adverse events and improved long-term survival. The HeartMate 3 is a centrifugal, continuous flow pump that is placed in the thorax and is engineered to be a more hemocompatible LVAS. This device is constructed with

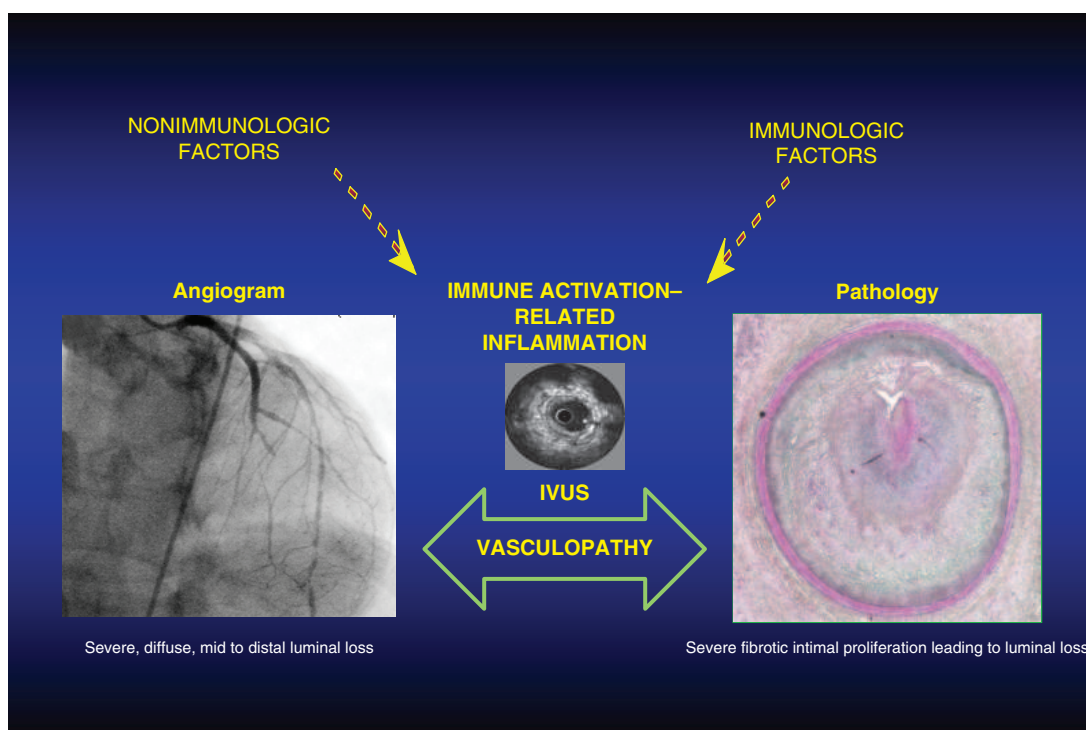


FIGURE 271-1 Cardiac allograft vasculopathy is initiated and propagated by the combined influence of immunologic and nonimmunologic insults on the allograft vasculature. An inflammatory milieu determines the development of diffuse, aggressive luminal blockages that in early forms exhibit intimal thickening and fibrosis. IVUS, intravascular ultrasound (can be used to diagnose early forms of intimal thickening).

a fully magnetically levitated motor, offers wider blood flow paths, and exhibits a fixed intrinsic pulse (by the motor ramping its speed up and down at 2-s intervals). These features have been shown to reduce rates of hemolysis and decrease the shearing of high-molecular-weight multimers of von Willebrand factor. This pump has been tested in the MOMENTUM 3 trial, which reported its final results in 1028 patients randomly allocated to either the HeartMate 3 pump or the HeartMate II LVAS. The fully magnetically levitated HeartMate 3 pump was associated with less frequent need for pump replacement than the HeartMate II device and was superior with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device. The need for pump replacement and occurrence of stroke of any severity, major bleeding, or gastrointestinal hemorrhage were lower in

the centrifugal-flow pump group than in the axial-flow pump group. Experience at 5 years with this LVAS has demonstrated an improved long-term survival (Fig. 271-2). This LVAS has been shown to nearly eliminate the complication of pump thrombosis and markedly reduce stroke rates, as well as decrease bleeding complications. Long-term follow-up with this pump has demonstrated a survival of nearly 60% at 5 years, which has been confirmed by real-world experience from registry analyses. In younger patients (<50 years) or those without comorbidity and an uncomplicated surgical course, the 5-year survival rivals that achieved with cardiac transplantation (75%). The patients for whom LVAS should ideally be employed include those with severe persistent systolic heart failure symptoms who have failed to respond to optimal medical management. Commonly, these patients have marked

A New Survival and Functional Status Benchmark with Contemporary LVAD Therapy

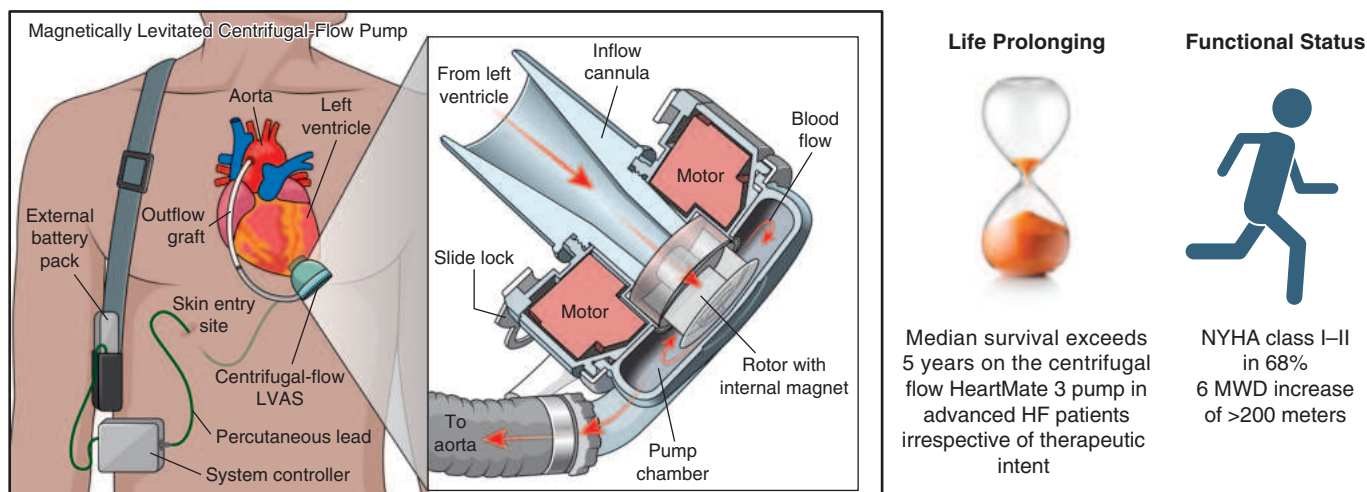


FIGURE 271-2 Due to the technological advances conferred by the HeartMate 3 pump, a new survival and functional status benchmark with contemporary left ventricular assist device (LVAD) therapy has been established. The centrifugal flow HeartMate 3 pump is frictionless and fully magnetically levitated, which does not induce hemolysis or pump thrombosis. This pump is associated with a median survival exceeding 5 years. 6 MWD, 6-min walk distance; HF, heart failure; NYHA, New York Heart Association. (Left illustration: reproduced with permission from MR Mehra et al: *N Engl J Med* 376:440, 2017.)

functional limitation indicated by a peak oxygen consumption of <12 mL/kg per min, or the patient is bound to continuous intravenous inotropic therapy owing to symptomatic hypotension or demonstrates worsening renal function or persistent refractory congestion. In such patients, despite improvements in medical therapy, the median survival is often less than 1 year, and substantial life prolongation can be anticipated with use of the HeartMate 3 LVAS. Currently, the role of LVAS in “less sick” patients (those with moderate symptoms) is less well supported since sufficient equipoise does not exist due to the need to be tethered to an external driveline that connects to a power source.

■ MANAGEMENT OF LVAS AND THEIR COMPLICATIONS

Continuous flow LVAS rely on pressure gradients between the left ventricular cavity and the aorta. As such, forward flow is critically dependent on management of systemic blood pressure. Due to the low pulsatile nature of the blood flow, blood pressure is measured by using a Doppler ultrasound (which measures mean or opening blood pressure, which is lower than the systolic blood pressure) since a peripheral pulse is usually not detectable. The ideal mean arterial blood pressure should be kept to ≤ 90 mmHg and antihypertensive drug therapy prescribed using renin-angiotensin-aldosterone system drugs or other vasodilators. The blood flow path through current devices results in increased shear stress, which may manifest in the form of low-grade hemolysis and the development of an acquired von Willebrand disease due to loss of high-molecular-weight multimers of von Willebrand factor. This hematologic aberration has been associated with a risk of gastrointestinal bleeding, particularly resulting from arteriovenous malformations in the intestines. Therefore, a common complication encountered in patients is that of an anemia, often due to iron deficiency.

The unsupported right ventricle often demonstrates worsening function and results in congestion requiring diuretic therapy. While unloading of the left ventricle decreases right-sided afterload, increased device flow results in a greater right heart preload, and effects of the LVAS on the septum reduce right ventricular contractile efficiency, leading to development of right ventricular dilatation and maladaptation between the right ventricle and pulmonary circuit. Cardiac arrhythmias are common in patients supported with LVAS and often

require antiarrhythmic therapy or ablation since such events can trigger low flow through the device.

Hemocompatibility-related adverse outcomes include neurologic events (ischemic and hemorrhagic strokes), device-related thrombosis leading to pump malfunction, and nonsurgical bleeding complications (Fig. 271-3). Elimination of aspirin as part of the antithrombotic regimen used (which includes a vitamin K antagonist targeting international normalized ratio to 2–3) has been shown to substantially reduce the risk of nonsurgical bleeding with consequent decrease in bleeding-related hospitalizations and cost of care. This outcome was demonstrated in the ARIES HM3 study with evidence of generalizability among most patients implanted with the HeartMate 3 LVAS. Strokes can occur with the HeartMate 3 LVAS and are generally noted during the surgical implant course with later occurrence in a manner similar to that observed for patients with advanced heart failure who are not supported with LVAS. This complication is an important reason for lack of adoption of device therapy in the less sick population. Another cause of morbidity with legacy devices was pump thrombosis requiring reoperation for device malfunction, which has been largely eliminated with the introduction of the HeartMate 3 LVAS. Lactate dehydrogenase is an excellent (although nonspecific) biomarker of hemolysis and can herald impending or established pump thrombosis, but this is uncommonly encountered except in circumstances where a circulating thrombus is entrained within the pump chamber. Patients who have suspected left ventricular assist device (LVAD) thrombosis and do not undergo LVAD exchange or cardiac transplantation have a high mortality rate, and reoperation (pump exchange) carries a modest perioperative mortality risk and is preferred as the therapy of choice, although this is extremely uncommon.

Infection is common, most often involving the driveline (the conduit connecting the device to the external controller and batteries), and occurs in 20–50% of patients following LVAS implant at 5 years. Such an infection is treated with local internal exploration and requires long-term suppressive antibiotics unless the patient undergoes cardiac transplantation or the device is exchanged. Infection and its inflammatory sequelae predispose to thrombosis and heighten the risk of neurologic complications, leading to a worsening milieu in hemocompatibility.

The Future of Bio-engineered LVADs

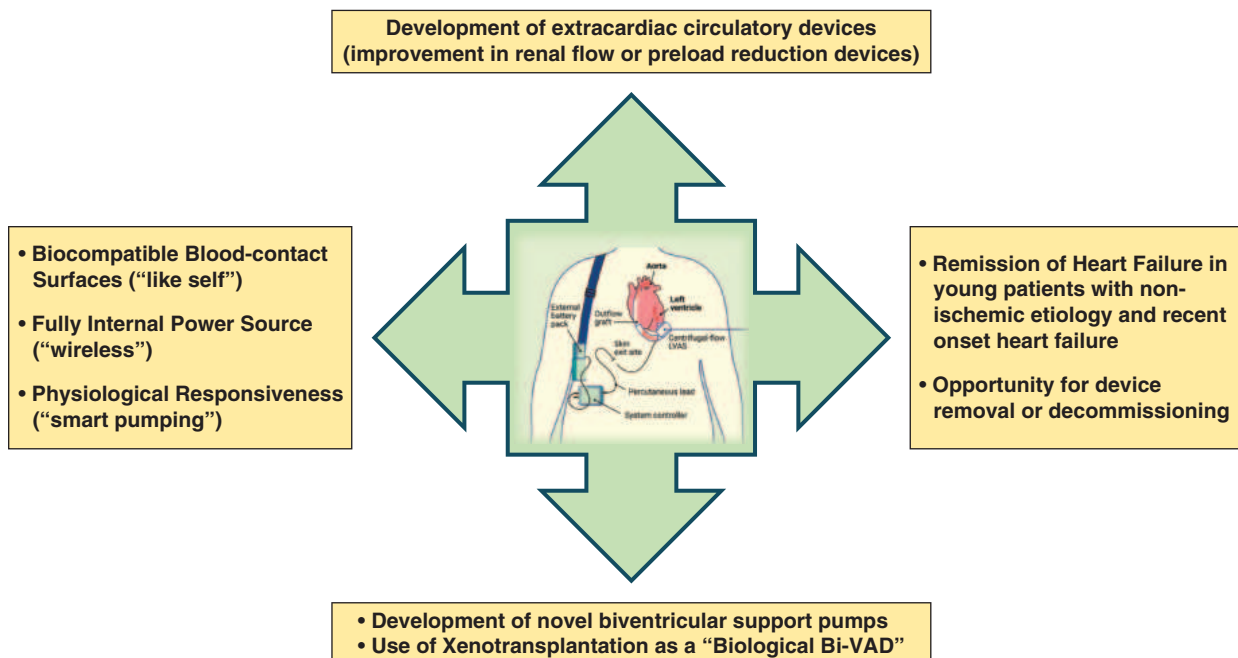


FIGURE 271-3 The future of bioengineered left ventricular assist devices (LVADs). Engineering advances will require development of more biocompatible and fully internally implanted systems with physiologic responsive function. (Adapted from Boulet J, Wanderley MRB Jr, Mehra MR. Contemporary Left Ventricular Assist Device Therapy as a Bridge or Alternative to Transplantation. *Transplantation* 108(6):1333-1341: 2024.)

■ NOVEL DEVICES

Newer pumps are in development that are designed to overcome challenges inherent in current-generation LVAS. Engineering continues to advance in this field, and we await devices that provide physiologic and synchronized pulsatile flow (rather than the unnatural transapical to aortic flow with current LVADs). The next paradigm shift will likely require a return to natural and pulsatile flow LVAS that are more biocompatible (as opposed to hemocompatible), responsive to physiologic requirements (smart pumps), and forgettable (without an external driveline to power its components).

■ TOTAL ARTIFICIAL HEART

Not all patients are candidates for an LVAS, particularly those with severe right-sided heart failure or conditions that do not allow placement of an LVAS (restrictive cardiomyopathy, cardiac amyloidosis, massive anterior myocardial infarction, complex congenital heart disease). In such patients, either a biventricular assist device approach or a total artificial heart pump can be considered. The SynCardia total artificial heart is a pulsatile, implantable pump that consists of two polyurethane ventricles with pneumatically driven diaphragms and four tilting disc valves. This requires excision of the native ventricles and thus cannot be employed as a myocardial recovery strategy. There are specific clinical issues that are unique to the total artificial heart management. This device operates on a steep physiologic curve and has little adaptability to tolerate either systemic blood pressure changes or large shifts in blood volume. As the ventricles are excised, most patients exhibit a sharp decline in renal function due to the loss of natriuretic peptide expression by the myocardium. Severe hemolysis is common due to the presence of four mechanical valves, and aberrant erythropoiesis is noted, leading to a severe anemia. Newer artificial hearts using biocompatible surfaces are under study (CARMAT), as well as those that use continuous flow technology (BIVACOR).

■ XENOTRANSPLANTATION

On January 7, 2022, the first genetically edited pig-to-human heart xenotransplantation was performed. The porcine xenograft was derived from a 10-gene edited animal with four genes that were knocked out (targeting three carbohydrate antigens associated with hyperacute rejection and one anticardiac growth gene) and six genes that were knocked in (targeting human complement regulation, coagulation, and anti-inflammatory pathways). Two transplants have been performed in living human recipients with limited survival of 2 months or less, with death occurring due to delayed graft dysfunction and subsequent loss. There are substantial ongoing concerns with continued immunologic barriers (despite gene modification), costs of donor organ development and recovery, ethical considerations, and considerations of transmission of zoonoses.

■ GLOBAL CONSIDERATIONS

While LVAS are available worldwide, their use and indications vary from country to country. In the United States, payers used to require discrete discrimination of indication into either a bridge to transplant or destination therapy, whereas in most European countries, this artificial segregation was not used. Cost-effectiveness studies suggest improvement with the newer devices, yet some countries only allow use of this technology as a bridge to transplantation (United Kingdom) while awaiting more definitive long-term studies for lifetime use. The use of LVAS in moderately symptomatic ambulatory patients with chronic systolic heart failure is still discouraged throughout the world, awaiting the availability of devices that can be fully internalized without the need for an external driveline. Globally, the rates of myocardial recovery allowing for decommissioning or removal of devices remain low, although in young patients with nonischemic heart failure of relatively recent onset, this could be an important consideration.

■ FURTHER READING

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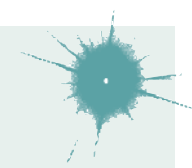
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272

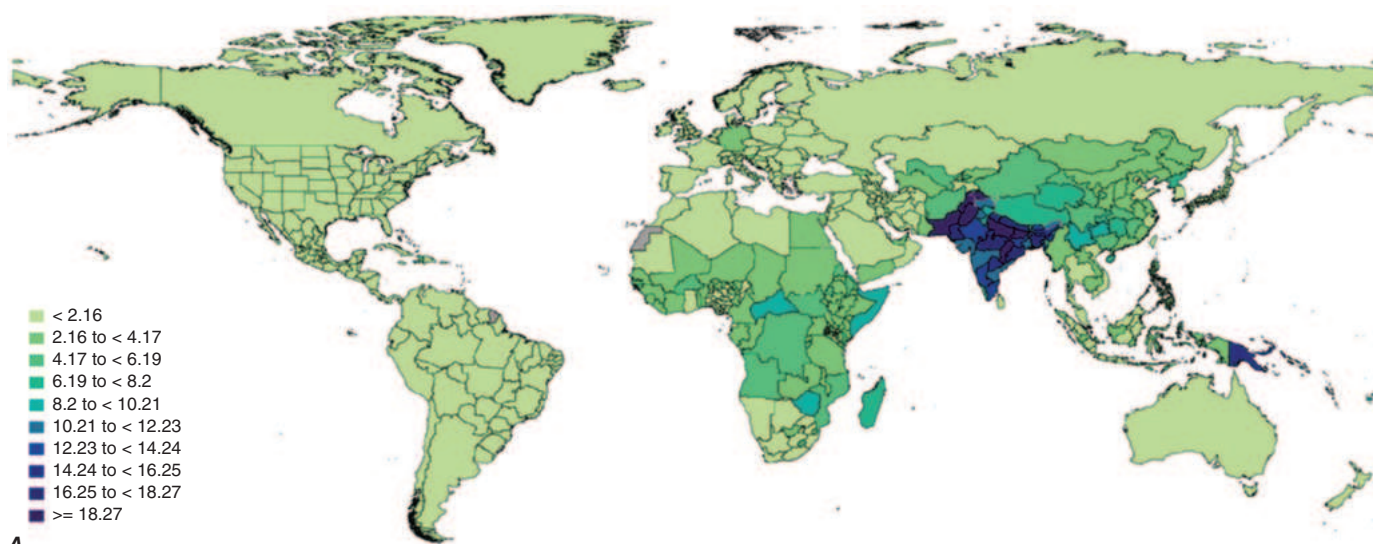
Aortic Stenosis

Patrick T. O'Gara, Joseph Loscalzo

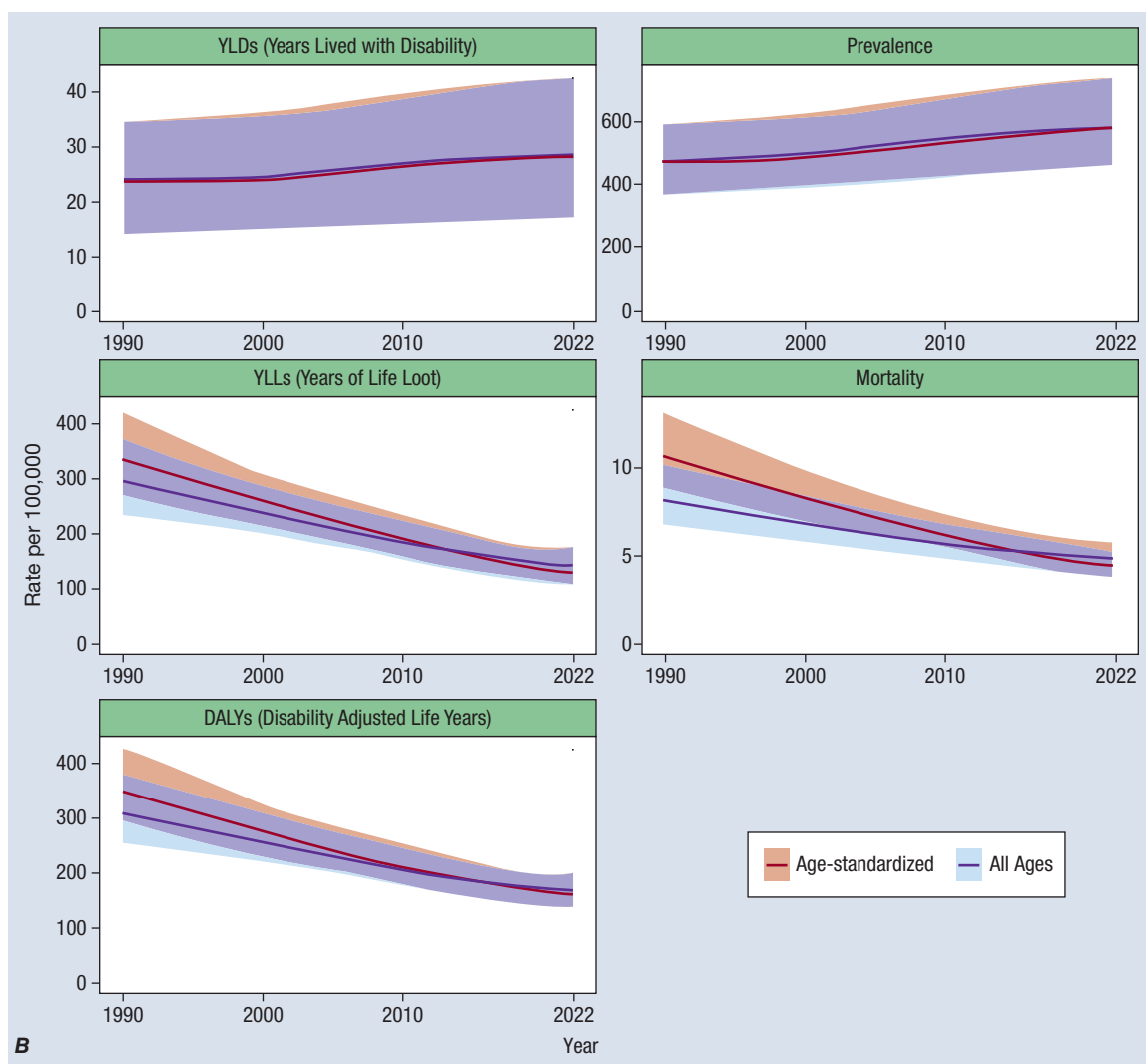


GLOBAL BURDEN OF VALVULAR HEART DISEASE

Valvular heart disease ranks well below ischemic heart disease, stroke, hypertension, obesity, and diabetes as a major threat to the public health. Nevertheless, it can cause significant morbidity and lead to premature death. Rheumatic fever ([Chap. 371](#)) is the dominant cause of valvular heart disease in low- and middle-income countries. Its prevalence has been estimated to range from as low as 1 per 100,000 school-age children in Costa Rica to as high as 150 per 100,000 in China ([Fig. 272-1](#)). Prevalence is higher among females than males, especially for individuals age 20–40 years. Rheumatic heart disease accounts for 12–65% of hospital admissions related to cardiovascular disease and 2–10% of hospital discharges in some endemic countries. Prevalence and mortality rates vary among communities even within the same country as a function of overcrowding, the availability of medical resources, education level, and population-wide programs for detection and treatment of group A streptococcal pharyngitis. In economically deprived areas, tropical and subtropical climates (particularly on the Indian subcontinent and in Southeast Asia), Central America, and the Middle East, rheumatic valvular disease progresses more rapidly than in more developed nations and frequently causes serious symptoms in patients aged <20 years. This accelerated natural history may be due to repeated infections with more virulent strains of rheumatogenic streptococci. Approximately 45–50 million people (575.5 per 100,000) live with rheumatic heart disease worldwide, an estimated prevalence characterized by 300,000 new cases and 233,000 case fatalities (5 per 100,000) per year, with the highest prevalence and age-adjusted mortality rates in sub-Saharan Africa, South Asia, Central Asia, and Oceania. In the United States, rheumatic heart disease accounted for 3876 deaths in 2020. Although globally the age-standardized mortality rate from rheumatic heart disease declined by nearly 50% between 1990 and 2022, the prevalence of heart failure attributable to rheumatic heart disease increased by nearly 90% over the same time interval.



A



B

FIGURE 272-1 The global burden of rheumatic heart disease. (A) Global map of age-standardized rheumatic heart disease mortality rate per 100,000 in 2022. Mortality rates are highest in South Asia and Oceania. **(B)** Global rheumatic heart disease estimates per 100,000 by measure with shaded 95% uncertainty interval, 1990–2022. DALYs, disability-adjusted life-years; YLDs, years lived with disability; YLLs, years of life lost. (Reproduced with permission from GA Mensah et al: Global burden of cardiovascular diseases and risks, 1990–2022. *J Am Coll Cardiol* 82:2350, 2023.)

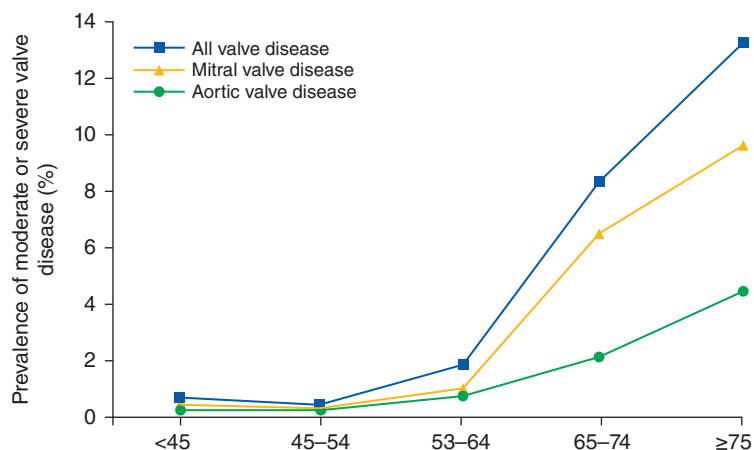


FIGURE 272-2 The burden of moderate or severe mitral and aortic valve disease in the United States. Prevalence estimates are derived from three population-based studies comprising a total of 11,911 individuals: The Coronary Artery Risk Development in Young Adults (CARDIA), the Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular Health Study (CHS). (Reproduced with permission from VT Nkomo, JM Gardin, TN Skelton, et al: Burden of valvular heart diseases: a population-based study, *Lancet* 368(9540):1005-1011, 2006.)

Valve disease in high-income countries is dominated by degenerative or nonrheumatic inflammatory processes that lead to valve thickening, fibrosis, calcification, and dysfunction. The prevalence of valvular heart disease increases significantly with age. Community echocardiographic screening identifies previously undiagnosed, predominantly mild valvular heart disease in ~50% of the population aged >65 years. In this age group, the prevalence of previously undiagnosed moderate or severe valvular heart disease is ~6%. Significant left-sided valve disease may affect as many as 12–13% of adults aged >75 years (Fig. 272-2). Severe aortic stenosis (AS) is estimated to affect 3.5% of the population aged >75 years. A Swedish epidemiologic study estimated the incidence of newly diagnosed valvular heart disease at 64 per 100,000 person-years, with approximately 70% of incident disease observed in individuals 65 years of age or older. AS and mitral regurgitation contributed approximately one-half and one-quarter, respectively, of the valvular heart disease diagnoses in this study.

The incidence of infective endocarditis (Chap. 133) has increased with the aging of the population, the more widespread prevalence of vascular grafts and intracardiac devices, the emergence of more virulent multidrug-resistant microorganisms, and the growing epidemic of injection drug use. North American age-standardized incidence rates for endocarditis increased from 10.1 per 100,000 population in 1990 to 12.54 per 100,000 population in 2019. The more restricted use of antibiotic prophylaxis since 2007 has not been convincingly associated with an increase in incidence rates for infective endocarditis cases attributable to oropharyngeal pathogens. Infective endocarditis has become a relatively more frequent cause of acute valvular regurgitation. Valve surgery during the acute phase of infective endocarditis is performed in ~50–60% of hospitalized patients. Duration of intravenous antibiotic use may be shortened in selected cases.

Bicuspid aortic valve (BAV) disease affects as many as 0.5–1.4% of the general population and is accompanied by an associated aortopathy in ~30–40% of individuals, a disease process expressed as root or ascending aortic aneurysm formation or descending thoracic aortic coarctation. An increasing number of childhood survivors of congenital heart disease present later in life with valvular dysfunction. The global burden of valvular heart disease will continue to progress.

As is true for many other chronic health conditions, disparities in access to and quality of care for patients with valvular heart disease have been well documented, especially for those patients with rheumatic heart disease in low- and middle-income countries. In the Society for Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) registry, black patients

compose <5% of patients in the United States who have received a transcatheter valve for AS. Management decisions and outcome differences based on age, sex, race, geography, and other social determinants of health require intensification of educational efforts and prioritization of resources.

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in Chaps. 44 and 246; of electrocardiography (ECG) in Chap. 247; of echocardiography and other noninvasive imaging techniques in Chap. 248; and of cardiac catheterization and angiography in Chap. 249.

AORTIC STENOSIS

AS is the most common valve lesion among adult patients with chronic valvular heart disease; the majority of adult patients with symptomatic, valvular AS are male.

ETIOLOGY AND PATHOGENESIS

(Table 272-1) AS in adults is due to degenerative calcification of the aortic cusps and occurs most commonly on a substrate of congenital disease (BAV), chronic (trileaflet) deterioration, or previous rheumatic inflammation. A pathologic study of specimens removed at the time of aortic valve replacement (AVR) for AS in adults showed that 53% were bicuspid and 4% were unicuspid. The process of aortic valve deterioration and calcification is not a passive one, but, rather, one that shares many features with vascular atherosclerosis, including endothelial dysfunction, lipid accumulation, inflammatory cell activation, cytokine release, and upregulation of several signaling pathways (Fig. 272-3). Eventually, a fibrocalcific response is established wherein collagen is deposited and valvular myofibroblasts differentiate phenotypically into osteoblasts and actively produce bone matrix proteins that allow for the deposition of calcium hydroxyapatite crystals. Genetic polymorphisms involving the vitamin D receptor, the estrogen receptor in postmenopausal women, interleukin 10, and apolipoprotein E4 have been linked to the development of calcific AS, and a strong familial clustering of cases with trileaflet valves has been reported from western France. Several traditional atherosclerotic risk factors have also been associated with the development and progression of calcific AS, including hypertension, low-density lipoprotein (LDL) cholesterol, lipoprotein(a) (Lp[a]), diabetes mellitus, smoking, chronic kidney disease, and the metabolic syndrome. In a Canadian observational cohort study, the incidence of severe AS was 144 per 100,000 person-years. Hypertension, diabetes mellitus, and dyslipidemia accounted for approximately one-third of the population-attributable risk for severe AS. The presence of aortic valve sclerosis (focal thickening and calcification of the leaflets not severe enough to cause obstruction) is associated with an excess risk of cardiovascular death and myocardial infarction (MI) among persons aged >65. Approximately 30% of persons aged >65 years exhibit some degree of aortic valve sclerosis. Rate and extent of progression to valve obstruction (stenosis) vary among individual patients.

Rheumatic disease of the aortic leaflets produces commissural fusion, sometimes resulting in a bicuspid-appearing valve. This condition, in turn, makes the leaflets more susceptible to trauma and ultimately leads to fibrosis, calcification, and further narrowing. By the time obstruction to left ventricular (LV) outflow causes serious clinical disability, the valve is usually a rigid calcified mass, and careful examination may make it difficult or even impossible to determine

TABLE 272-1 Major Causes of Aortic Stenosis

VALVE LESION	ETIOLOGIES
Aortic stenosis	Congenital (bicuspid, unicuspid) Degenerative calcific disease Rheumatic fever Radiation

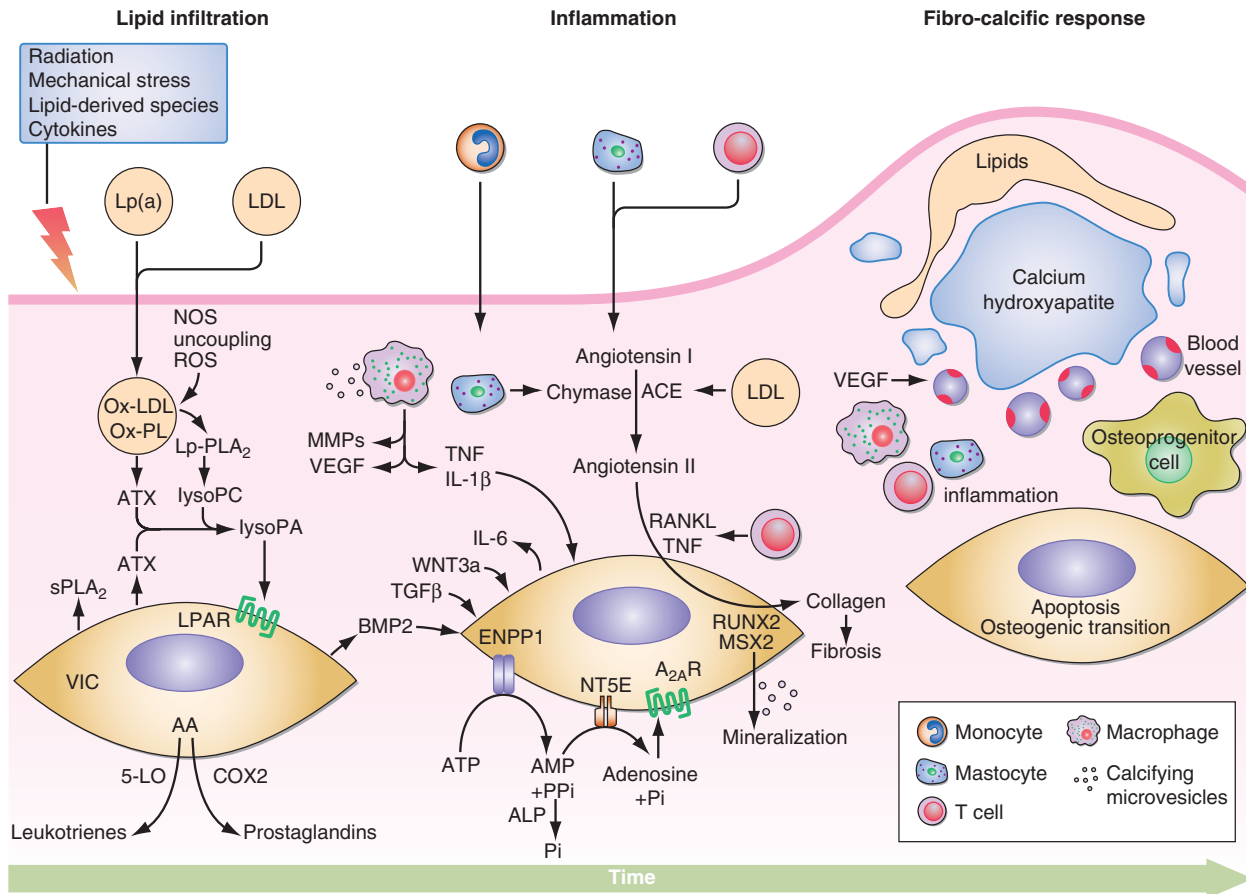


FIGURE 272-3 Pathogenesis of calcific aortic stenosis. Lipid and inflammatory cell infiltration occurs across damaged endothelium. A cascade of events follows that leads eventually to formation of disorganized collagen (fibrosis) and calcium hydroxyapatite (bone) deposition. Valvular interstitial cells (VIC) are critical participants in this active process. AA, arachidonic acid; ACE, angiotensin-converting enzyme; ALP, alkaline phosphatase; ApoB, apolipoprotein B; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ATX, autotaxin; A_{2A}R, adenosine A_{2A} receptor; BMP, bone morphogenetic protein; COX2, cyclooxygenase 2; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase; IL, interleukin; 5-LO, 5-lipoxygenase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPAR, lysophosphatidic acid receptor; Lp-PLA₂, lipoprotein-associated phospholipase A₂; lysoPA, lysophosphatidic acid; lysoPC, lysophosphatidylcholine; MMP, matrix metalloproteinase; NOS, nitric oxide synthase; Ox-PL, oxidized phospholipid; Ox-LDL, oxidized LDL; RANKL, receptor activator of nuclear factor- κ B ligand; ROS, reactive oxygen species; RUNX2, runt-related transcription factor 2; sPLA₂, secreted PLA₂; TGF β , transforming growth factor β ; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VIC, valvular interstitial cell. (Reproduced with permission from B Lindman et al: *Calcific aortic stenosis*. *Nat Rev Dis Primers* 2:16006, 2016.)

the etiology of the underlying process. Rheumatic AS is almost always associated with involvement of the mitral valve and with aortic regurgitation (AR). Mediastinal radiation can also result in late scarring, fibrosis, and calcification of the aortic leaflets. In this context, the calcification process also affects the mitral annulus.

■ BICUSPID AORTIC VALVE DISEASE

A bicuspid aortic valve (BAV) is the most common congenital heart valve defect and occurs in 0.5–1.4% of the population with a 2–4:1 male-to-female predominance. The inheritance pattern appears to be autosomal dominant with incomplete penetrance, although some have questioned an X-linked component as suggested by the prevalence of BAV disease among patients with Turner's syndrome. The prevalence of BAV disease among first-degree relatives of an affected individual is ~10%. A single gene defect to explain the majority of cases has not been identified, although mutations in the *NOTCH1*, *GATA5*, and *GATA4* genes have been described in some families. Abnormalities in endothelial nitric oxide synthase and NKX2.5 have been implicated as well. Medial degeneration with ascending aortic aneurysm formation occurs commonly among patients with BAV disease; aortic coarctation is less frequently encountered. Patients with BAV disease have larger aortas than patients with comparable tricuspid aortic valve disease. The aortopathy develops independently of the hemodynamic severity of the valve lesion, but directional shear forces dictated by the anatomic configuration of the valve appear to influence its expression. For example, enlargement of the

ascending aorta along its greater curvature is most often associated with right-left cusp fusion (Sievers classification type 1), the most common bicuspid variant. Patients with BAV disease are at risk for aneurysm formation and/or dissection. A BAV can be a component of more complex congenital heart disease with or without other left heart obstructing lesions, as seen in Shone's complex (supravalvular mitral membrane, parachute mitral valve, subvalvular AS, and aortic coarctation).

■ OTHER FORMS OF OBSTRUCTION TO LEFT VENTRICULAR OUTFLOW

In addition to valvular AS, three other lesions may be responsible for obstruction to LV outflow: *hypertrophic obstructive cardiomyopathy* (Chaps. 266–270), *discrete fibromuscular/membranous subaortic stenosis*, and *supravalvular AS* (Chap. 280). The causes of LV outflow obstruction can usually be differentiated on the basis of the cardiac examination and Doppler echocardiographic findings.

■ PATHOPHYSIOLOGY

The obstruction to LV outflow produces a systolic pressure gradient between the LV and aorta. When severe obstruction is suddenly produced experimentally, the LV responds by dilation and reduction of stroke volume. However, in some patients, the obstruction may be present at birth and/or increase gradually over the course of many years, and LV contractile performance is maintained by the presence of concentric LV hypertrophy. Initially, this serves as an adaptive

mechanism because it reduces toward normal the systolic stress developed by the myocardium, as predicted by the Laplace relation wall tension normalized to wall thickness ($S = Pr/h$, where S = systolic wall stress, P = pressure, r = radius, and h = wall thickness). A large transaortic valve pressure gradient may exist for many years without a reduction in cardiac output (CO) or the development of LV dilation. Ultimately, however, excessive hypertrophy becomes maladaptive, LV systolic function declines because of afterload mismatch, abnormalities of diastolic function progress, and irreversible myocardial fibrosis develops.

A mean systolic pressure gradient >40 mmHg with a normal CO or an effective aortic orifice area of <1 cm² (or <0.6 cm²/m² body surface area in a normal-sized adult)—i.e., less than approximately one-third of the normal orifice area—is generally considered to represent severe obstruction to LV outflow. The elevated LV end-diastolic pressure observed in many patients with severe AS and preserved ejection fraction (EF) signifies the presence of diminished compliance of the hypertrophied LV. Although the CO at rest is within normal limits in most patients with severe AS, it usually fails to rise normally during exercise. Loss of an appropriately timed, vigorous atrial contraction, as occurs in atrial fibrillation (AF) or atrioventricular dissociation, may cause rapid progression of symptoms. Late in the course, contractile function deteriorates because of afterload excess, the CO and LV-aortic pressure gradient declines, and the mean left atrial (LA), pulmonary artery (PA), and right ventricular (RV) pressures rise. LV performance can be further compromised by superimposed epicardial coronary artery disease (CAD). Stroke volume (and thus CO) can also be reduced in patients with significant hypertrophy and a small LV cavity despite a normal EF. Low-flow (defined as a stroke volume index <35 mL/m²), low-gradient (defined as a mean pressure gradient <40 mmHg) AS (with either reduced or normal LV systolic function) is both a diagnostic and therapeutic challenge.

The hypertrophied LV causes an increase in myocardial oxygen requirements. In addition, even in the absence of obstructive CAD, coronary blood flow is impaired to the extent that ischemia can be precipitated under conditions of excess demand. Capillary density is reduced relative to wall thickness, compressive forces are increased, and the elevated LV end-diastolic pressure reduces the coronary driving pressure. The subendocardium is especially vulnerable to ischemia by this mechanism.

■ SYMPTOMS

AS is rarely of clinical importance until the valve orifice has narrowed to ~ 1 cm². Even severe AS may exist for many years without producing any symptoms because of the ability of the hypertrophied LV to generate the elevated intraventricular pressures required to maintain a normal stroke volume. Once symptoms occur, or the LV ejection fraction falls below normal, valve replacement is indicated.

Most patients with pure or predominant AS have gradually increasing obstruction over years but do not become symptomatic until the sixth to eighth decades. Adult patients with BAV disease, however, develop significant valve dysfunction and symptoms one to two decades sooner. Exertional dyspnea, angina pectoris, and syncope are the three cardinal symptoms. Often, there is a history of insidious progression of fatigue and dyspnea associated with gradual curtailment of activities and reduced effort tolerance. *Dyspnea* results primarily from elevation of the pulmonary capillary pressure caused by elevations of LV diastolic pressures secondary to impaired relaxation and reduced LV compliance. *Angina pectoris* usually develops somewhat later and reflects an imbalance between the increased myocardial oxygen requirements and reduced oxygen availability. CAD may or may not be present, although its coexistence is common among AS patients age >65 . *Exertional syncope* may result from a decline in arterial pressure caused by vasodilation in exercising muscles and inadequate vasoconstriction in nonexercising muscles in the face of a fixed CO, or from a sudden fall in CO produced by an arrhythmia.

Because the CO at rest is usually well maintained until late in the course, marked fatigability, weakness, peripheral cyanosis, cachexia, and other clinical manifestations of a low CO are usually not prominent until this stage is reached. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, i.e., symptoms of LV failure, also occur only in the advanced stages of the disease. Severe pulmonary hypertension leading to RV failure and systemic venous hypertension, hepatomegaly, AF, and tricuspid regurgitation (TR) are usually late findings in patients with isolated severe AS.

When AS and mitral stenosis (MS) coexist, the reduction in flow (CO) caused by MS lowers the pressure gradient across the aortic valve and, thereby, masks many of the clinical findings produced by AS. The transaortic pressure gradient can be increased in patients with concomitant AR due to higher aortic valve flow rates.

■ PHYSICAL FINDINGS

The heart rhythm is generally regular until late in the course; at other times, AF should suggest the possibility of associated mitral valve disease. Hypertension occurs commonly among older adults with AS. In the late stages, however, when stroke volume declines, the systolic pressure may fall and the pulse pressure narrow. The carotid arterial pulse rises slowly to a delayed peak (*pulsus parvus et tardus*). A thrill or anacrotic “shudder” may be palpable over the carotid arteries, more commonly the left. In the elderly, the stiffening of the arterial wall may mask this important physical sign. In many patients, the *a* wave in the jugular venous pulse is accentuated. This results from the diminished distensibility of the RV cavity caused by the bulging, hypertrophied interventricular septum.

The LV impulse is sometimes displaced laterally in the later stages of the disease. A double apical impulse (with a palpable S_4) may be appreciated, particularly with the patient in the left lateral recumbent position. A systolic thrill may be present at the base of the heart to the right of the sternum when leaning forward or in the suprasternal notch.

Auscultation An early systolic ejection sound is frequently audible in children, adolescents, and young adults with congenital BAV disease. This sound usually disappears when the valve becomes calcified and rigid. As AS increases in severity, LV systole may become prolonged so that the aortic valve closure sound no longer precedes the pulmonic valve closure sound, and the two components may become synchronous, or aortic valve closure may even follow pulmonic valve closure, causing paradoxical splitting of S_2 (Chap. 246). The sound of aortic valve closure can be heard most frequently in patients with AS who have pliable valves; calcification diminishes the intensity of this sound. Frequently, an S_1 is audible at the apex and reflects the presence of LV hypertrophy and an elevated LV end-diastolic pressure; an S_3 generally occurs late in the course when the LV dilates and its systolic function becomes severely compromised.

The murmur of AS is described as an ejection (mid) systolic murmur that commences shortly after the S_1 , increases in intensity to reach a peak toward the middle of ejection, and ends just before aortic valve closure. It is characteristically low-pitched, rough, and rasping in character, and loudest at the base of the heart, most commonly in the second right intercostal space. It is transmitted upward along the carotid arteries. Occasionally, it is transmitted downward and to the apex, where it may be confused with the systolic murmur of mitral regurgitation (MR) (Gallavardin effect). In almost all patients with severe obstruction and preserved CO, the murmur is at least grade III/VI. In patients with mild degrees of obstruction or in those with severe stenosis with heart failure and low CO in whom the stroke volume and, therefore, the transvalvular flow rate are reduced, the murmur may be relatively soft and brief.

■ LABORATORY EXAMINATION

ECG In most patients with severe AS, there is LV hypertrophy. In advanced cases, ST-segment depression and T-wave inversion (LV “strain”) in standard leads I and aVL and in the left precordial leads are evident. However, there is no close correlation between the ECG

and the hemodynamic severity of obstruction, and the absence of ECG signs of LV hypertrophy does not exclude severe obstruction. Systemic hypertension can coexist and also contribute to the development of hypertrophy.

Echocardiogram The key findings on transthoracic echocardiogram are thickening, calcification, and reduced systolic opening of the aortic valve leaflets and LV hypertrophy. Eccentric closure of the aortic valve cusps is characteristic of congenitally bicuspid valves. Transesophageal echocardiography imaging can display the obstructed orifice extremely well, but it is not routinely required for accurate characterization of AS. The valve gradient and aortic valve area can be estimated by Doppler measurement of the transaortic velocity. Severe AS is defined by a valve area $<1 \text{ cm}^2$, whereas moderate AS is defined by a valve area of $1\text{--}1.5 \text{ cm}^2$ and mild AS by a valve area of $1.6\text{--}2 \text{ cm}^2$. Aortic valve sclerosis, conversely, is accompanied by a jet velocity of $<2.5 \text{ m/s}$ (peak gradient $<25 \text{ mmHg}$). LV dilation and reduced systolic shortening reflect impairment of LV function. There is a robust experience with the use of longitudinal strain to characterize earlier changes in LV systolic function before a decline in EF can be appreciated. Doppler indices of impaired diastolic function are frequently seen. The frequency with which echocardiography should be repeated during follow-up is dictated by the severity of the stenosis (Table 272-2).

Echocardiography is useful for identifying coexisting valvular abnormalities, differentiating valvular AS from other forms of LV outflow obstruction, and measuring the aortic root and proximal ascending aortic dimensions. These aortic measurements are particularly important for patients with BAV disease. Dobutamine stress echocardiography can be useful for the evaluation of patients with AS and severe LV systolic dysfunction (low-flow, low-gradient, severe AS with reduced EF), in whom the severity of the AS can often be difficult to judge. Patients with severe AS (i.e., valve area $<1 \text{ cm}^2$) with a relatively low mean gradient ($<40 \text{ mmHg}$) despite a normal EF (low-flow, low-gradient, severe AS with normal EF) are often hypertensive, and efforts to control their systemic blood pressure should be optimized before Doppler echocardiography is repeated. The use of dobutamine stress echocardiography in this setting is not advised. When there is continued uncertainty regarding the severity of AS in patients with reduced CO and reduced or normal LVEF, quantitative analysis of the amount of aortic valve calcium with chest computed tomography (CT) can be helpful. Aortic valve calcium scores that define severe AS differ for men and women, as men tend to have relatively more calcification and women more fibrosis of the valve leaflets. There is increasing use of chest CT angiography to assess aortic valve morphology and function. It has become the imaging method of choice to plan for transcatheter aortic valve implantation (TAVI). Finally, the use of cardiac magnetic resonance (CMR) imaging to screen for the presence of increased extracellular volume (interstitial fibrosis) and late gadolinium enhancement (replacement fibrosis) in patients with severe AS is an area of active investigation. Future management pathways related to the asymptomatic AS patient are likely to include an integrated assessment of the findings from multimodality imaging studies.

Chest X-Ray The chest x-ray may show no or little overall cardiac enlargement for many years. Hypertrophy without dilation may produce some rounding of the cardiac apex in the frontal projection and slight backward displacement in the lateral view. A dilated

proximal ascending aorta may be seen along the upper right heart border in the frontal view. Aortic valve calcification may be discernible in the lateral view, but it is usually readily apparent on fluoroscopic examination or by echocardiography; the absence of valvular calcification on fluoroscopy in an adult suggests that severe valvular AS is *not* present. In later stages of the disease, as the LV dilates, there is increasing roentgenographic evidence of LV enlargement, pulmonary congestion, and enlargement of the LA, PA, and right-sided heart chambers.

Catheterization Right- and left-sided heart catheterization for invasive assessment of AS is performed infrequently but can be useful when there is a discrepancy between the clinical and noninvasive findings. Concern has been raised that attempts to cross the aortic valve for measurement of LV pressures are associated with a risk of cerebral embolization. Catheterization can also be useful in three distinct categories of patients: (1) *patients with multivalvular disease*, in whom the role played by each valvular deformity should be defined to aid in the planning of operative treatment; (2) *young, asymptomatic patients with noncalcific congenital AS*, to define the severity of obstruction to LV outflow, because operation or percutaneous aortic balloon valvuloplasty (PABV) may be indicated in these patients if severe AS is present, even in the absence of symptoms; and (3) *patients in whom it is suspected that the obstruction to LV outflow may not be at the level of the aortic valve but rather at the sub- or supravalvular level*.

Coronary angiography is indicated to screen for CAD in appropriate patients with severe AS who are being considered for surgical or transcatheter valve intervention. Angiography can be performed invasively at the time of catheterization for hemodynamic assessment or with noninvasive CT techniques. Decision-making regarding the need for coronary artery revascularization at the time of aortic valve intervention is individualized.

NATURAL HISTORY

Death in patients with severe AS occurs most commonly in the seventh and eighth decades. Based on data obtained at postmortem examination in patients before surgical treatment became widely available, the average time to death after the onset of various symptoms was as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; and heart failure, 1.5–2 years. Moreover, in $>80\%$ of patients who died with AS, symptoms had existed for <4 years. Among adults dying with valvular AS, sudden death, which presumably resulted from an arrhythmia, occurred in 10–20%; however, most sudden deaths occurred in patients who had previously been symptomatic. Sudden death as the first manifestation of severe AS is very uncommon ($\sim 1\%$ per year) in asymptomatic adult patients. Calcific AS is a progressive disease, with an annual reduction in valve area averaging 0.1 cm^2 and annual increases in peak jet velocity and mean valve gradient averaging 0.3 m/s and 7 mmHg , respectively.

TREATMENT

Aortic Stenosis (Fig. 272-4)

MEDICAL TREATMENT

In patients with severe AS (valve area $<1 \text{ cm}^2$), strenuous physical activity and competitive sports should be avoided, even in the asymptomatic stage. Care must be taken to avoid dehydration and hypovolemia to protect against a significant reduction in CO. Medications used for the treatment of hypertension or CAD, including beta blockers and angiotensin-converting enzyme (ACE) inhibitors, are generally safe for asymptomatic patients with preserved LV systolic function. Control of blood pressure is important to attenuate the deleterious pathophysiologic effects of two resistance circuits (valve, arterial circulation) in series. Nitroglycerin is helpful in relieving angina pectoris in patients with CAD. Neither HMG-CoA reductase inhibitors (“statins”) nor

TABLE 272-2 Frequency of Follow-Up Echocardiography in Aortic Stenosis

STAGE OF DISEASE	FREQUENCY OF ECHOCARDIOGRAPHY
Progressive (stage B)	Every 3–5 years (mild severity, V_{max} $2.0\text{--}2.9 \text{ m/s}$) Every 1–2 years (moderate severity, V_{max} $3.0\text{--}3.9 \text{ m/s}$)
Severe asymptomatic (stage C1)	Every 6–12 months (V_{max} $>4 \text{ m/s}$)

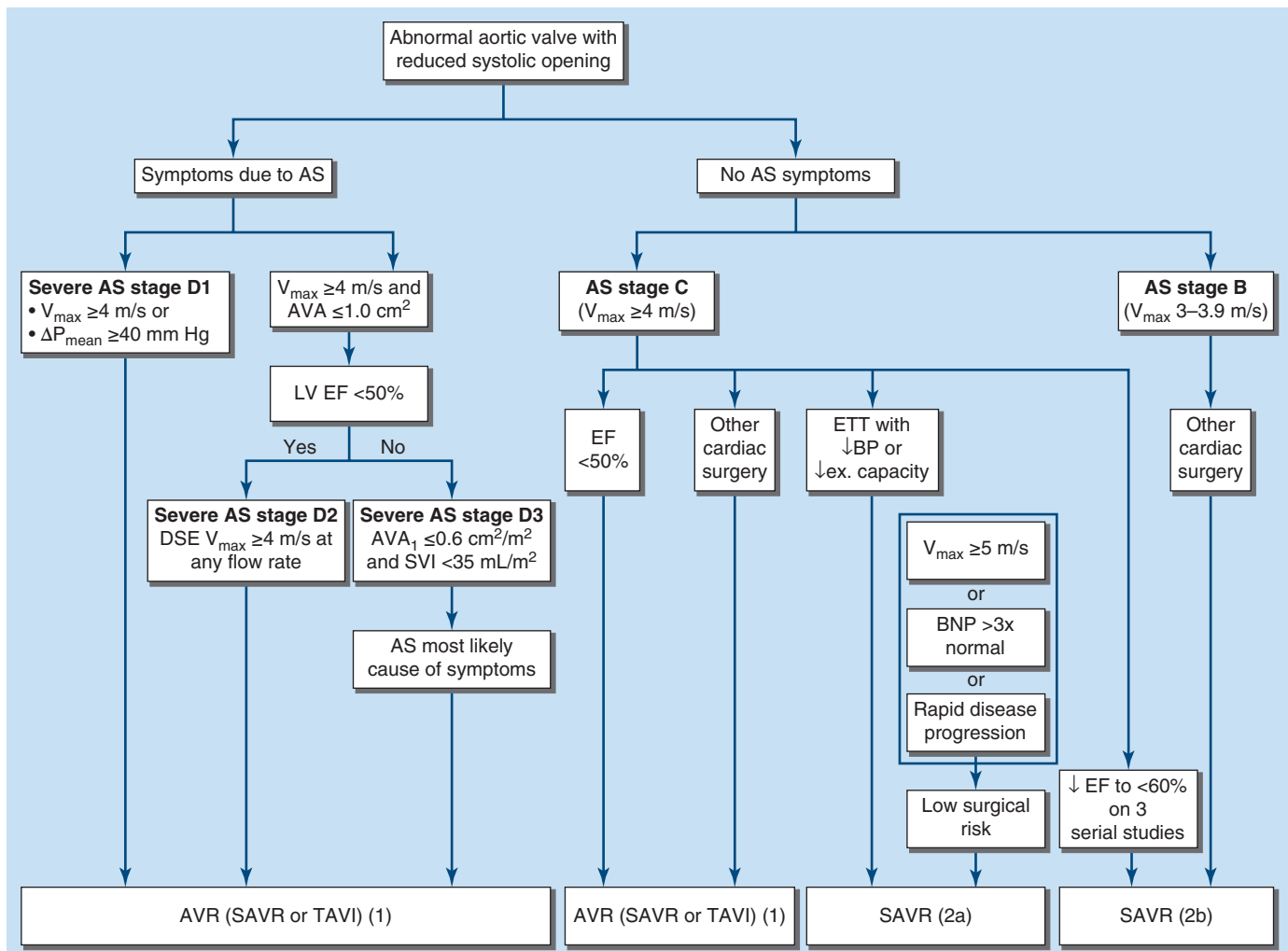


FIGURE 272-4 Management strategy for patients with aortic stenosis. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored with clinical and echocardiographic follow-up. The class designations refer to the American Heart Association/American College of Cardiology methodology for treatment recommendations. Class I recommendations should be performed or are indicated; Class IIa recommendations are considered reasonable to perform; Class IIb recommendations may be considered. The stages refer to the stages of progression of the disease. At disease stage A, risk factors are present for the development of valve dysfunction; stage B refers to progressive, mild-moderate, asymptomatic valve disease; stage C disease is severe in nature but clinically asymptomatic; stage C1 characterizes asymptomatic patients with severe valve disease but compensated ventricular function; stage C2 refers to asymptomatic, severe disease with ventricular decompensation; stage D refers to severe, symptomatic valve disease. With aortic stenosis, stage D1 refers to symptomatic patients with severe aortic stenosis and a high valve gradient (>40 mmHg mean gradient); stage D2 comprises patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and low left ventricular ejection fraction (LVEF); and stage D3 characterizes patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and preserved LVEF (paradoxical, low-flow, low-gradient severe aortic stenosis). Patients with symptomatic severe AS (left side of the diagram, jet velocity ≥ 4 m/s) should be referred for AVR (SAVR or TAVI). Asymptomatic patients with severe AS (jet velocity ≥ 4 m/s) should be referred for AVR (SAVR or TAVI) for LVEF $<50\%$ or when other cardiac surgery is needed (e.g., aneurysm repair). There are several findings for which referral for AVR would be reasonable related to results of exercise testing, the presence of a jet velocity >5 m/s, or elevated B-type natriuretic peptide (BNP), provided the patient is considered low risk for complications related to AVR. AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BP, blood pressure; DSE, dobutamine stress echocardiography; EF, ejection fraction; ETT, exercise treadmill test; ΔP_{mean} , mean pressure gradient; SAVR, surgical AVR; TAVI, transcatheter aortic valve implantation; V_{max} , maximum velocity. (Reproduced with permission from CM Otto et al: 2020 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 143(5):e72, 2021.)

inhibitors of the renin-angiotensin-aldosterone system slow the rate of progression of AS. The use of statin medications should be driven by considerations regarding primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events. Studies with agents targeted to Lp(a) are ongoing. The need for endocarditis prophylaxis is restricted to AS patients with a prior history of endocarditis.

SURGICAL TREATMENT

Asymptomatic patients with calcific AS and severe obstruction should be followed carefully for the development of symptoms and for evidence of deteriorating LV function on serial echocardiography. Operation is indicated in patients with severe AS (valve area

<1 cm² or 0.6 cm²/m² body surface area) who are symptomatic, those who exhibit LV systolic dysfunction (EF $<50\%$), and those with AS due to BAV disease and an aneurysmal root or ascending aorta (maximal dimension >5.5 cm). Operation for aneurysm disease is recommended at smaller aortic diameters (4.5–5.0 cm) for patients with a family history of an aortic catastrophe and for patients who exhibit rapid aneurysm growth (>0.5 cm/year). Patients with asymptomatic moderate or severe AS who are referred for coronary artery bypass grafting surgery should also have AVR. The majority ($\sim 80\%$) of patients with symptomatic severe AS referred for surgery are considered low risk for perioperative death or major complication. Operative risk increases as a function of age, comorbidities, and the need for concomitant aortic or other heart valve surgery or coronary artery bypass grafting. A 2023

analysis from the STS Adult Cardiac Surgery Database reported a 5-year survival rate of 95% following isolated surgical AVR (SAVR) in low-risk AS patients of mean age 74 years. The indications for SAVR in the asymptomatic patient have been the subject of intense debate, as surgical outcomes in selected patients have continued to improve. Relative indications for which surgery is reasonable include an abnormal response to treadmill exercise; rapid progression of AS, especially when urgent access to medical care might be compromised; very severe AS, defined by an aortic valve jet velocity >5 m/s or mean gradient >60 mmHg; excessive LV hypertrophy in the absence of systemic hypertension; and a brain natriuretic peptide level >3 times the upper reference limit, with low surgical risk. Exercise testing can be safely performed in asymptomatic patients, as many as one-third of whom will show signs of functional impairment. In a small randomized controlled trial (RCT) of early surgery versus conservative care for asymptomatic patients with very severe AS (defined by a transaortic valve jet velocity ≥ 4.5 m/s, mean gradient ≥ 50 mmHg, or aortic valve area ≤ 0.75 cm²), the rate of operative death or death from cardiovascular causes during follow-up was reduced with early surgery. In the conservative care group, the cumulative incidence of sudden death was 4% at 4 years and 14% at 8 years. In another randomized trial of early surgery versus conservative care for asymptomatic patients with lesser degrees of AS (jet velocity ≥ 4 m/s, mean gradient ≥ 40 mmHg, aortic valve areas ≤ 1.0 cm²) and normal LV systolic function, early surgery resulted in a significant reduction in a composite endpoint of death, MI, stroke, and heart failure hospitalization.

Operation should be carried out promptly (1–3 months) after symptom onset. Clinical decision-making is straightforward for patients with normal-flow (>35 mL/m²), high-gradient (≥ 40 mmHg) severe AS. In patients with low-flow, low-gradient severe AS with reduced LVEF, perioperative mortality rates are high (15–20%), and evidence of LV dysfunction usually persists even after a technically successful operation. Long-term postoperative survival correlates with preoperative LV function. Nonetheless, in view of the even worse prognosis of such patients when they are treated medically, there is usually little choice but to advise valve replacement, especially in patients in whom flow reserve can be demonstrated by dobutamine stress echocardiography (defined by a $\geq 20\%$ increase in stroke volume after dobutamine challenge). Patients in this high surgical risk group are treated with TAVI whenever feasible (see below), but robust data from RCTs in this subpopulation of severe AS patients are lacking. The management of patients with low-flow, low-gradient severe AS with normal LVEF is also challenging. Outcomes are improved with surgery or TAVI compared with conservative care for symptomatic patients with this type of “paradoxical” low-flow AS, but more research is needed to guide therapeutic decision-making for individual patients. In patients in whom severe AS and CAD coexist, relief of the AS and revascularization may sometimes result in striking clinical and hemodynamic improvement.

Because many patients with calcific AS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary function before AVR is recommended. Age alone is not a contraindication to SAVR for AS. The perioperative mortality rate depends to a substantial extent on the patient's preoperative clinical and hemodynamic state. Assessment of frailty is a critical component of preprocedural evaluation. Treatment decisions for AS patients who are not at low operative risk are made by a multidisciplinary heart team with representation from general cardiology, interventional cardiology, multimodality imaging, cardiac surgery, and other subspecialties as needed, including geriatrics. The 8-year survival rate of older adult (mean age 74), low surgical risk patients following isolated SAVR is 85–90%. Recommendations regarding the type of valve prosthesis (biological or mechanical) must weigh the trade-offs between limited bioprosthetic valve durability and the risks of thromboembolism and bleeding with a mechanical valve and are heavily influenced by patient age, expected longevity, and individual preferences. Bioprostheses are

generally favored for patients age >65 years. Shared decision-making with younger patients must be individualized, although increasing numbers of patients age <65 now opt for a biological valve replacement. Approximately 10–20% of bioprosthetic valves evidence primary valve failure by 15 years, requiring re-replacement (or valve-in-valve TAVI, see below), and an approximately equal percentage of patients with mechanical prostheses develop hemorrhagic complications as a consequence of treatment with vitamin K antagonists. In a large observational study of patients who underwent SAVR in California between 1996 and 2013, receipt of a biological versus a mechanical prosthesis in patients <55 years old was associated with an excess hazard of death over 15 years of follow-up. Homograft AVR is usually reserved for patients with aortic valve endocarditis.

The Ross procedure involves replacement of the diseased aortic valve with the autologous pulmonic valve and implantation of a homograft in the native pulmonic position. It is a technically complex procedure that may be considered in selected young or middle-aged adult patients when surgical and institutional expertise are available. Late postoperative complications include aortic root dilation, AR, and pulmonary homograft stenosis.

PERCUTANEOUS AORTIC BALLOON VALVULOPLASTY

This procedure is preferable to operation in many children and young adults with congenital, noncalcific AS (**Chap. 280**). It is not recommended as definitive therapy in adults with severe calcific AS because of a very high restenosis rate (80% within 1 year) and the risk of procedural complications, although on occasion, it has been used successfully as a bridge to operation or TAVI in patients with severe LV dysfunction and shock. It is performed routinely as part of the TAVI procedure (see below).

TRANSCATHETER AORTIC VALVE IMPLANTATION

TAVI surpassed SAVR for treatment of isolated AS in the United States in 2016 and is now available to symptomatic patients across the entire surgical risk spectrum (prohibitive, high, intermediate, and low) on the basis of the favorable results observed in a series of landmark RCTs reported over the past decade. The results of a randomized trial of TAVI versus conventional care in asymptomatic AS patients will be released around 2024–2025. TAVI is most commonly performed using one of two systems, a balloon-expandable valve (BEV) or a self-expanding valve (SEV), both of which incorporate a pericardial bioprosthesis (**Fig. 272-5A, B**). TAVI is most frequently undertaken via the transfemoral route, although trans-LV apical, subclavian, carotid, and ascending aortic routes have been used. Nonfemoral access is associated with higher complication rates. Aortic balloon valvuloplasty under rapid RV (or LV) pacing is performed as a first step to create an orifice of sufficient size for the prosthesis. Procedural success rates exceed 95% in appropriately selected patients. Among low surgical risk patients with symptomatic severe AS, randomized trials with follow-up through 4–5 years have demonstrated similar valve performance and clinical outcomes for SAVR versus TAVI using either a BEV or SEV platform (**Fig. 272-6**). Outcomes achieved with TAVI technology have been very favorable and have allowed the extension of AVR to groups of patients previously considered poor candidates for conventional surgery. Nevertheless, some prohibitive or high surgical risk patients are not candidates for this procedure because their comorbidity profile, frailty, and expected longevity would make its undertaking inappropriate. The heart team is specifically charged with making challenging decisions of this nature. The use of these devices for treatment of patients with structural deterioration of bioprosthetic aortic valves (valve-in-valve TAVI), as an alternative to reoperative valve replacement, has increased sharply over the past 5 years. The technology has also been increasingly applied to selected BAV patients despite the fact that patients with this anatomy were excluded from the landmark RCTs.



FIGURE 272-5 Balloon-expandable (A) and self-expanding (B) valves for transcatheter aortic valve replacement (TAVR). B, inflated balloon; N, nose cone; V, valve. (Part A, courtesy of Edwards Lifesciences, Irvine, CA; with permission. NovaFlex+ is a trademark of Edwards Lifesciences Corporation. Part B, © Medtronic, Inc. 2015. Medtronic CoreValve Transcatheter Aortic Valve. CoreValve is a registered trademark of Medtronic, Inc.)

Compared with SAVR, transfemoral TAVI results in fewer peri-procedural deaths and confers lower risks of strokes, major bleeding, and AF. Hospital lengths of stay are significantly shorter and return to normal activity more rapid with TAVI. Rates of permanent pacemaker use, perivalvular AR, bioprosthetic leaflet thrombosis, and vascular complications are lower with SAVR. The choice between TAVI versus SAVR for patients with trileaflet AS who

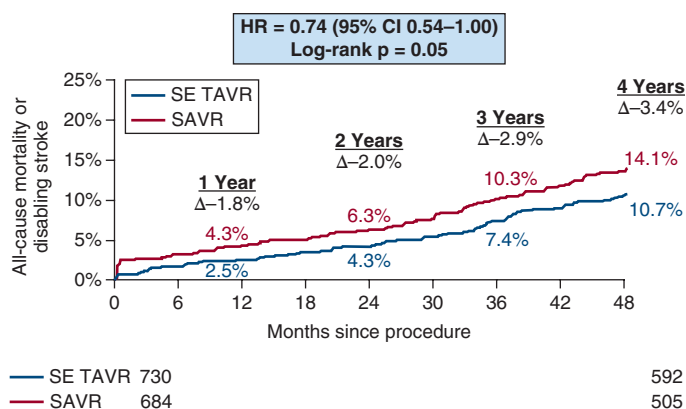


FIGURE 272-6 Four-year cumulative incidence of all-cause mortality or disabling stroke for low surgical risk aortic stenosis patients assigned to self-expanding transcatheter aortic valve implantation (SE-TAVR; n = 730) or surgical aortic valve replacement (SAVR; n = 684). In this study, TAVR was noninferior to SAVR and marginally superior to SAVR for the combined endpoint. (Reproduced with permission from JK Forrest et al: 4-year outcomes of patients with aortic stenosis in the EVOLUT low risk trial. *J Am Coll Cardiol* 82:2163, 2023.)

prefer a biological prosthesis rests on several clinical, imaging, and technical considerations (Fig. 272-7 and Table 272-3). Because there are scant RCT data on TAVI outcomes in patients <65 years, SAVR is recommended in this age group. Aortic valve/root anatomy, as well as the extent, severity, and distribution of calcium, and the distance of the coronary arteries from the plane of the annulus, may dictate a surgical approach, as could the need to perform a concomitant procedure such as ascending aortic replacement. Lastly, inability to achieve transfemoral access is a relative impediment to TAVI given the higher complication rates observed when this procedure is undertaken from other vascular access sites.

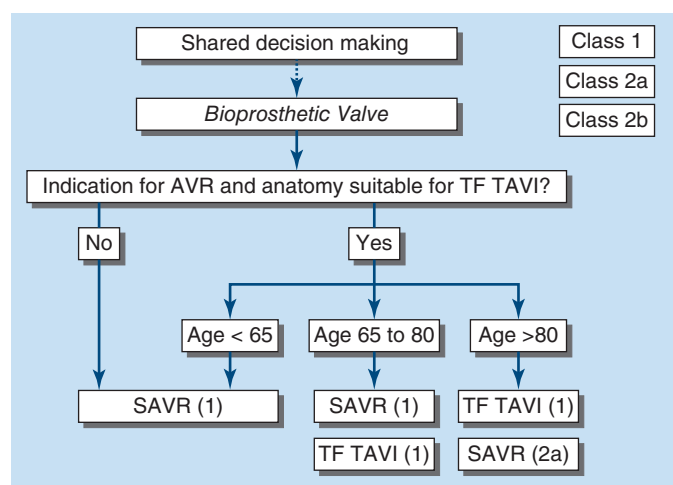


FIGURE 272-7 Suggested decision-making algorithm for the elective choice of transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for aortic stenosis patients with an indication for valve intervention. The pathway emphasizes the premium placed on transfemoral (TF) TAVI access and the age-related differences in recommendations. Patients younger than age 65 are recommended to undergo SAVR given the paucity of prospective randomized data on intermediate- and long-term TAVI outcomes for individuals younger than age 70. AVR, aortic valve replacement. (Reproduced and abridged with permission from CM Otto et al: 2020 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 143:e72, 2021.)

TABLE 272-3 Factors Favoring SAVR, TAVI, or Palliative Care in Patients with Aortic Stenosis

	FAVORS SAVR	FAVORS TAVI	FAVORS PALLIATION
Age/life expectancy ^a	Younger age/longer life expectancy	Older age/fewer expected remaining years of life	Limited life expectancy
Valve anatomy	Bicuspid aortic valve Subaortic (LVOT) calcification Rheumatic valve disease Small or large aortic annulus ^b	Calcific trileaflet AS	
Prosthetic valve preference	Mechanical or surgical bioprosthetic valve preferred Concern for patient-prosthesis mismatch (annular enlargement might be considered)	Bioprosthetic valve preferred Favorable ratio of life expectancy to valve durability TAVI provides larger valve area than same-sized SAVR	
Concurrent cardiac conditions	Aortic dilation ^c Severe primary MR Severe CAD requiring bypass grafting Septal hypertrophy requiring myectomy Atrial fibrillation	Severe calcification of the ascending aorta ("porcelain" aorta)	Irreversible severe LV systolic dysfunction Severe MR due to annular calcification
Noncardiac conditions		Severe lung, liver, or renal disease Mobility issues (high risk for sternotomy)	Symptoms likely due to noncardiac conditions Severe dementia Moderate to severe involvement of 2 or more other organ systems
Frailty	Not frail or few frailty measures	Frailty likely to improve after TAVI	Severe frailty unlikely to improve after TAVI
Estimated risk of SAVR or TAVI	SAVR risk low TAVI risk high	TAVI risk low to medium SAVR risk high to prohibitive	Prohibitive SAVR risk (>15%) or post-TAVI life expectancy <1 year
Procedure-specific impediments	Valve anatomy, annular size, or low coronary ostial height precludes TAVI Vascular access does not allow transfemoral TAVI	Previous cardiac surgery with at-risk coronary grafts Previous chest irradiation	Valve anatomy, annular size, or coronary ostial height precludes TAVI Vascular access does not allow transfemoral TAVI
Goals of care and patient preferences and values	Less uncertainty about valve durability Avoid repeat intervention Lower risk of permanent pacer Life prolongation Symptom relief Improved long-term exercise capacity and QOL Avoid vascular complications Accepts longer hospital stay, pain in recovery period	Accepts uncertainty about valve durability and possible repeat intervention Higher risk of permanent pacer Life prolongation Symptom relief Improved exercise capacity and QOL Prefers shorter hospital stay, less postprocedure pain	Life prolongation not an important goal Avoid futile or unnecessary diagnostic or therapeutic procedures Avoid procedural stroke risk Avoid possibility of cardiac pacer

^aData on bioprosthetic valve durability are more robust for SAVR valves than for TAVI valves. Mechanical valves are very durable but require lifelong anticoagulation. Choice of prosthesis is a shared decision-making process accounting for individual patient values and preferences. ^bSurgical root enlargement can be performed at time of SAVR to allow a use of a larger prosthesis and reduce the occurrence of prosthesis-patient mismatch. ^cAortic root or ascending aortic enlargement may require surgical correction at time of SAVR.

Abbreviations: AS, aortic stenosis; CAD, coronary artery disease; LV, left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; QOL, quality of life; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Source: Reproduced with permission from CR Burke et al: Goals of care in patients with severe aortic stenosis. *Eur Heart J* 41:929, 2020.

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■ ETIOLOGY

(Table 273-1) Aortic regurgitation (AR) may be caused by primary valve disease, aortic root disease, or their combination.

Primary Valve Disease Rheumatic disease results in thickening, deformity, and shortening of the individual aortic valve cusps, changes that prevent their proper opening during systole and closure during diastole. A rheumatic origin is much less common in patients with isolated AR who do not have associated rheumatic mitral valve disease. Patients with congenital bicuspid aortic valve (BAV) disease may develop predominant AR, and ~20% of these patients will require aortic valve surgery between 10 and 40 years of age. Congenital fenestrations of the aortic valve occasionally produce mild AR. Membranous subaortic stenosis results in a high-velocity systolic jet that often leads to thickening and scarring of the aortic valve leaflets and secondary AR. Prolapse of an aortic cusp, resulting in progressive chronic AR, occurs in ~15% of patients with ventricular septal defect (Chap. 280), but may also occur as an isolated phenomenon or as a consequence of myxomatous degeneration sometimes associated with mitral and/or tricuspid valve involvement.

AR may result from infective endocarditis (IE), which can develop on a valve previously affected by rheumatic disease, a congenitally deformed valve, or on a normal aortic valve, and may lead to perforation or destruction of one or more leaflets. The aortic valve leaflets may become scarred and retracted during the course of syphilis or ankylosing spondylitis and contribute further to the AR that derives primarily from associated root dilation. Although traumatic rupture or avulsion of an aortic cusp is an uncommon cause of acute AR, it represents the most frequent serious lesion in patients surviving nonpenetrating cardiac injuries. The coexistence of hemodynamically significant aortic stenosis (AS) with AR usually excludes all the rarer forms of AR because it occurs almost exclusively in patients with rheumatic or congenital AR. In patients with AR due to primary valvular disease, dilation of the aortic annulus may occur secondarily and lead to worsening regurgitation.

Primary Aortic Root Disease AR also may be due entirely to marked aortic annular dilation, i.e., aortic root disease, without primary involvement of the valve leaflets; widening of the aortic annulus and lack of diastolic coaptation of the aortic leaflets are responsible for the AR (Chap. 291). Medial degeneration of the ascending aorta,

which may or may not be associated with other manifestations of Marfan’s syndrome; idiopathic dilation of the aorta; annuloaortic ectasia; osteogenesis imperfecta; and severe, chronic hypertension may all widen the aortic annulus and lead to progressive AR. Occasionally AR is caused by retrograde dissection of the aorta involving the aortic annulus. Syphilis and ankylosing spondylitis, both of which may also affect the aortic leaflets, may be associated with cellular infiltration and scarring of the media of the thoracic aorta, leading to aortic dilation, aneurysm formation, and severe regurgitation. In syphilis of the aorta (Chap. 187), now a very rare condition, the involvement of the intima may narrow the coronary ostia, which in turn may be responsible for myocardial ischemia. Takayasu’s aortitis and giant cell aortitis can also result in aneurysm formation and secondary AR.

■ PATHOPHYSIOLOGY

The total stroke volume ejected by the left ventricle (LV) (i.e., the sum of the effective forward stroke volume and the volume of blood that regurgitates back into the LV) is increased in patients with AR. In patients with severe AR, the volume of regurgitant flow may equal the effective forward stroke volume. In contrast to MR, in which a portion of the LV stroke volume is delivered into the low-pressure left atrium (LA), in AR, the entire LV stroke volume is ejected into a high-pressure zone, the aorta. An increase in the LV end-diastolic volume (increased preload) constitutes the major hemodynamic compensation for AR. The dilation and eccentric hypertrophy of the LV allow this chamber to eject a larger stroke volume without requiring any increase in the relative shortening of each myofibril. Therefore, severe AR may occur with a normal effective forward stroke volume and a normal LV ejection fraction (LVEF, total [forward plus regurgitant] stroke volume/end-diastolic volume), together with an elevated LV end-diastolic pressure and volume. However, through the operation of Laplace’s law, LV dilation increases the LV systolic tension required to develop any given level of systolic pressure. Chronic AR is, thus, a state in which LV preload and afterload are both increased. Ultimately, these adaptive measures fail. As LV function deteriorates, the end-diastolic volume rises further and the forward stroke volume and ejection fraction (EF) decline. Deterioration of LV function often precedes the development of symptoms. Considerable thickening of the LV wall also occurs with chronic AR, and at autopsy, the hearts of these patients may be among the largest encountered, sometimes weighing >1000 g.

The reverse diastolic pressure gradient from aorta to LV, which drives the AR flow, decreases progressively during diastole, accounting for the typical decrescendo nature of the diastolic murmur. Equilibration between aortic and LV pressures may occur toward the end of diastole in patients with chronic severe AR, particularly when the heart rate is slow. In patients with acute severe AR, the LV is unprepared for the regurgitant volume load. LV compliance is normal or reduced, and LV diastolic pressures rise rapidly, occasionally to levels >40 mmHg. The LV pressure may exceed the LA pressure toward the end of diastole, and this reversed pressure gradient closes the mitral valve prematurely.

In patients with chronic severe AR, the effective forward cardiac output (CO) usually is normal or only slightly reduced at rest, but often it fails to rise normally during exercise. An early sign of LV dysfunction is a reduction in the EF. In advanced stages, there may be considerable elevation of the LA, pulmonary artery (PA) wedge, PA, and right ventricular (RV) pressures and reduced forward CO at rest.

Myocardial ischemia may occur in patients with AR because myocardial oxygen requirements are elevated by LV dilation, hypertrophy, and elevated LV systolic tension, and coronary blood flow may be compromised. A large fraction (the majority) of coronary blood flow occurs during diastole, when aortic pressure is low, thereby reducing coronary perfusion or driving pressure. This combination of increased oxygen demand and reduced supply may cause myocardial ischemia, particularly of the subendocardium, even in the absence of epicardial coronary artery disease (CAD).

■ HISTORY

Approximately three-fourths of patients with pure or predominant valvular AR are men; women predominate among patients with primary

TABLE 273-1 Major Causes of Aortic Regurgitation

VALVE LESION	ETIOLOGIES
Aortic regurgitation	Valvular
	Congenital (bicuspid) Endocarditis Rheumatic fever Myxomatous (prolapse) Radiation Trauma Syphilis Ankylosing spondylitis
	Aortic root disease
	Aortic dissection Medial degeneration Marfan syndrome Bicuspid aortic valve Nonsyndromic familial aneurysm Aortitis Hypertension

valvular AR who have associated rheumatic mitral valve disease. A history compatible with IE may sometimes be elicited from patients with rheumatic or congenital involvement of the aortic valve, and the infection often precipitates or seriously aggravates preexisting symptoms.

In patients with *acute severe AR*, as may occur in IE, aortic dissection, or trauma, the LV cannot dilate sufficiently to maintain stroke volume, and LV diastolic pressure rises rapidly with associated marked elevations of LA and PA wedge pressures. Pulmonary edema and/or cardiogenic shock may develop rapidly.

Chronic severe AR may have a long latent period, and patients may remain relatively asymptomatic for as long as 10–15 years. Uncomfortable awareness of the heartbeat, especially on lying down, may be an early complaint. Sinus tachycardia, during exertion or with emotion, or premature ventricular contractions may produce particularly uncomfortable palpitations as well as head pounding. These complaints may persist for many years before the development of exertional dyspnea, usually the first symptom of diminished cardiac reserve. The dyspnea is followed by orthopnea, paroxysmal nocturnal dyspnea, and excessive diaphoresis. Anginal chest pain even in the absence of CAD may occur in patients with severe AR, even in younger patients. Anginal pain may develop at rest as well as during exertion. Nocturnal angina may be a particularly troublesome symptom, and it may be accompanied by marked diaphoresis. The anginal episodes can be prolonged and often do not respond satisfactorily to sublingual nitroglycerin. Systemic fluid accumulation, including congestive hepatomegaly and ankle edema, may develop late in the course of the disease.

■ PHYSICAL FINDINGS

In chronic severe AR, the jarring of the entire body and the bobbing motion of the head with each systole can be appreciated, and the abrupt distention and collapse of the larger arteries are easily visible. The examination should be directed toward the detection of conditions predisposing to AR, such as bicuspid valve, IE, Marfan's syndrome, or ankylosing spondylitis.

Arterial Pulse A rapidly rising “water-hammer” pulse, which collapses suddenly as arterial pressure falls rapidly during late systole and diastole (Corrigan's pulse), and capillary pulsations, an alternate flushing and paling of the skin at the root of the nail while pressure is applied to the tip of the nail (Quincke's pulse), are characteristic of chronic severe AR. A booming “pistol-shot” sound can be heard over the femoral arteries (Traube's sign), and a to-and-fro murmur (Duroziez's sign) is audible if the femoral artery is lightly compressed with a stethoscope.

The arterial pulse pressure is widened as a result of both systolic hypertension and a lowering of the diastolic pressure. The measurement of arterial diastolic pressure with a sphygmomanometer may be complicated by the fact that systolic sounds are frequently heard with the cuff completely deflated. However, the level of cuff pressure at the time of muffling of the Korotkoff sounds (phase IV) generally corresponds fairly closely to the true intra-arterial diastolic pressure. As the disease progresses and the LV end-diastolic pressure rises, the arterial diastolic pressure may actually rise as well, because the aortic diastolic pressure cannot fall below the LV end-diastolic pressure. For the same reason, acute severe AR may also be accompanied by only a slight widening of the pulse pressure. Such patients are invariably tachycardic as the heart rate increases in an attempt to preserve the CO.

Palpation In patients with chronic severe AR, the LV impulse is heaving and displaced laterally and inferiorly. The systolic expansion and diastolic retraction of the apex are prominent. A diastolic thrill may be palpable along the left sternal border in thin-chested individuals, and a prominent systolic thrill may be palpable in the suprasternal notch and transmitted upward along the carotid arteries. This systolic thrill and the accompanying murmur do not necessarily signify the coexistence of AS. In some patients with AR or with combined AS and AR, the carotid arterial pulse may be bisferiens, i.e., with two systolic waves separated by a trough (see Fig. 246-2C).

Auscultation In patients with severe AR, the aortic valve closure sound (A_2) is usually absent. A systolic ejection sound is audible in

patients with BAV disease, and occasionally an S_3 also may be heard. The murmur of chronic AR is typically a high-pitched, blowing, decrescendo diastolic murmur, heard best in the third intercostal space along the left sternal border (see Fig. 246-5B). In patients with mild AR, this murmur is brief, but as the severity increases, it generally becomes louder and longer, indeed holodiastolic. When the murmur is soft, it can be heard best with the diaphragm of the stethoscope and with the patient sitting up, leaning forward, and with the breath held in forced expiration. In patients in whom the AR is caused by primary valvular disease, the diastolic murmur is usually louder along the left than the right sternal border. However, when the murmur is louder along the right sternal border, it suggests that the AR is caused by aneurysmal dilation of the aortic root. “Cooing” or musical diastolic murmurs suggest eversion of an aortic cusp vibrating in the regurgitant stream.

A mid-systolic ejection murmur is frequently audible in isolated AR. It is generally heard best at the base of the heart and is transmitted along the carotid arteries. This murmur may be quite loud without signifying aortic valve obstruction. A third murmur sometimes heard in patients with severe AR is the *Austin Flint murmur*, a soft, low-pitched, rumbling mid-to-late diastolic murmur. It is probably produced by the diastolic displacement of the anterior leaflet of the mitral valve by the AR stream and is not associated with hemodynamically significant mitral valve obstruction. The auscultatory features of AR are intensified by strenuous and sustained handgrip, which augments systemic vascular resistance and increases LV afterload.

In acute severe AR, the elevation of LV end-diastolic pressure may lead to early closure of the mitral valve, a soft S_3 , a pulse pressure that is not particularly wide, and a soft, short, early diastolic murmur of AR.

■ LABORATORY EXAMINATION

ECG In patients with chronic severe AR, ECG signs of LV hypertrophy are common (Chap. 247). In addition, these patients frequently exhibit ST-segment depression and T-wave inversion in leads I, aVL, V_3 , and V_6 (“LV strain”). Left axis deviation and/or QRS prolongation may also be present.

Echocardiogram (Fig. 273-1) LV size is increased in chronic AR, and systolic function is normal or even supernormal until myocardial contractility declines, as signaled by a decrease in EF or increase in the end-systolic dimension. A rapid, high-frequency diastolic fluttering of the anterior mitral leaflet produced by the impact of the regurgitant jet is a characteristic finding. The echocardiogram is also useful in determining the cause of AR, by detecting dilation of the aortic annulus and root, aortic dissection or primary leaflet pathology. With severe AR, the central jet width assessed by color flow Doppler imaging exceeds 65% of the width of the LV outflow tract, the regurgitant volume is ≥ 60 mL/beat, the regurgitant fraction is $\geq 50\%$, and there is diastolic flow reversal in the proximal portion of the descending thoracic aorta. The continuous-wave Doppler profile of the AR jet shows a rapid deceleration time in patients with acute severe AR, due to the rapid increase in LV diastolic pressure. Surveillance transthoracic echocardiography (TTE) forms the cornerstone of longitudinal follow-up and allows for the early detection of changes in LV size and/or function. Assessment of LV global longitudinal strain (GLS; a measure of myocardial thickening in systole) with speckle track imaging may demonstrate changes in LV systolic function that precede a fall in EF. There is increasing experience with the use of three-dimensional echocardiography to measure LV volumes. Transesophageal echocardiography (TEE) can provide detailed anatomic assessment of the valve, root, and portions of the aorta. For patients in whom TTE is limited by poor acoustical windows or inadequate characterization of LV function or the cause or severity of the regurgitation, cardiac magnetic resonance (CMR) imaging can be performed. This modality also allows for accurate assessment of LV volumes, as well as aortic size and contour. It can also be utilized to screen for increased LV interstitial (extracellular volume fraction) and replacement fibrosis (late gadolinium enhancement). Both CMR imaging and cardiac computed tomography (CT) can also provide detailed assessment of aortic valve, root, and thoracic aortic anatomy.

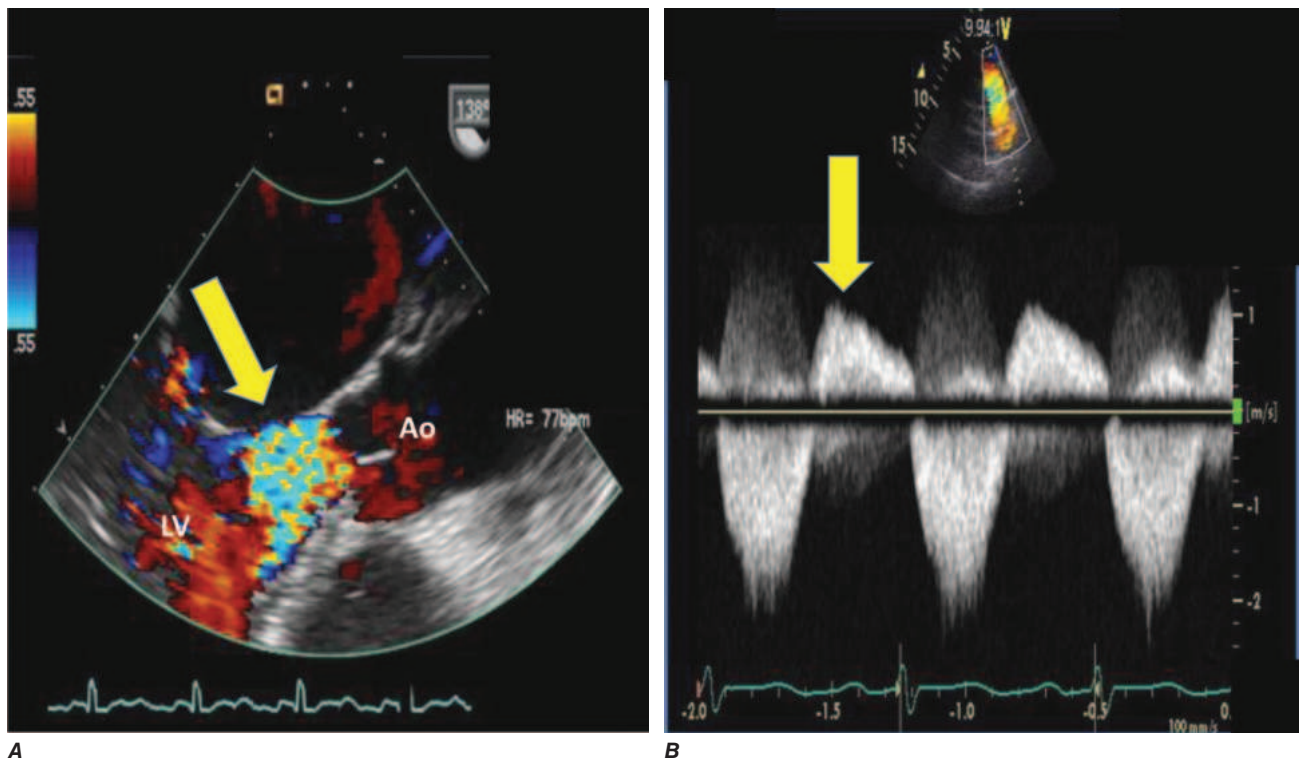


FIGURE 273-1 Echocardiographic and Doppler depiction of severe aortic regurgitation. (A) Color flow transesophageal echocardiographic long axis image in diastole shows a broad jet of severe aortic regurgitation (AR, yellow arrow) directed into the left ventricle. ECG rhythm strip below. Ao, aorta; BPM, beats per minute; HR, heart rate; LV, left ventricle. **(B)** Continuous wave Doppler tracing (middle image) obtained from the suprasternal window (top image) during transthoracic echocardiography shows dense, holodiastolic flow reversal in the descending thoracic aorta (yellow arrow) indicative of severe AR. ECG rhythm strip below.

Chest X-Ray In chronic severe AR, the apex is displaced downward and to the left in the frontal projection. In the left anterior oblique and lateral projections, the LV is displaced posteriorly and encroaches on the spine. When AR is caused by primary disease of the aortic root, aneurysmal dilation of the aorta may be noted, and the aorta may fill the retrosternal space in the lateral view. Echocardiography, CMR imaging, and chest CT angiography are more sensitive than a chest x-ray for the detection of root and ascending aortic enlargement.

Cardiac Catheterization and Angiography When needed, right and left heart catheterization with contrast aortography can provide confirmation of the magnitude of regurgitation and the status of LV function. Coronary angiography is performed routinely in patients at risk of coronary artery disease prior to surgery, although this anatomic information can also be obtained in many patients with coronary CT angiography.

TREATMENT

Aortic Regurgitation

ACUTE AORTIC REGURGITATION (FIG. 273-2)

Patients with acute severe AR may respond to intravenous diuretics and vasodilators (such as sodium nitroprusside), but stabilization is usually short-lived and operation is indicated urgently. Intra-aortic balloon counterpulsation is contraindicated. Beta blockers are best avoided so as not to reduce the CO further or slow the heart rate, thus allowing more time for diastolic filling of the LV. Surgery is the treatment of choice and is usually necessary within 24 h of diagnosis.

CHRONIC AORTIC REGURGITATION

The onset of symptoms, or LV systolic dysfunction, is an indication for surgery. Medical treatment with diuretics and vasodilators (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers [ARBs], dihydropyridine calcium channel blockers, or hydralazine) may be useful as a temporizing measure. Surgery

can then be performed in a more controlled setting. The use of vasodilators to extend the compensated phase of chronic severe AR in asymptomatic patients before the onset of symptoms or the development of LV dysfunction is not useful, although these agents should be employed to treat hypertension (systolic blood pressure >140 mmHg). It is often difficult to achieve adequate blood pressure control because of the increased stroke volume and enhanced LV ejection that accompany severe AR. Cardiac arrhythmias and systemic infections are poorly tolerated in patients with severe AR and must be treated promptly and vigorously. Although nitroglycerin and long-acting nitrates are not as helpful in relieving anginal pain as they are in patients with coronary heart disease, they are worth a trial. Patients with syphilitic aortitis should receive a full course of penicillin therapy (**Chap. 187**). Beta blockers and the ARB losartan may be useful to retard the rate of aortic root enlargement in young patients with Marfan's syndrome and aortic root dilation. A randomized controlled trial showed no difference in efficacy between atenolol and losartan for this indication. Whether beta blockers or ARBs are useful in retarding the rate of growth of aortic aneurysms in other patient subsets (e.g., BAV disease with aortopathy, Takayasu's disease) has not been demonstrated. Beta blockers in patients with valvular AR were previously considered relatively contraindicated due to concern that slowing of the heart rate would allow more time for diastolic regurgitation and LV filling. Observational reports, however, have suggested that beta blockers may provide functional benefit in some patients with chronic AR. Beta blockers can sometimes provide incremental blood pressure lowering in patients with chronic AR and hypertension. They can also lessen the sense of forceful heart action that many patients find uncomfortable. Patients with severe AR, particularly those with an associated aortopathy, should avoid isometric exercises.

SURGICAL TREATMENT

In deciding on the advisability and proper timing of surgical treatment, two points should be kept in mind: (1) patients with chronic severe AR usually do not become symptomatic until *after* the development of myocardial dysfunction; and (2) when delayed too long

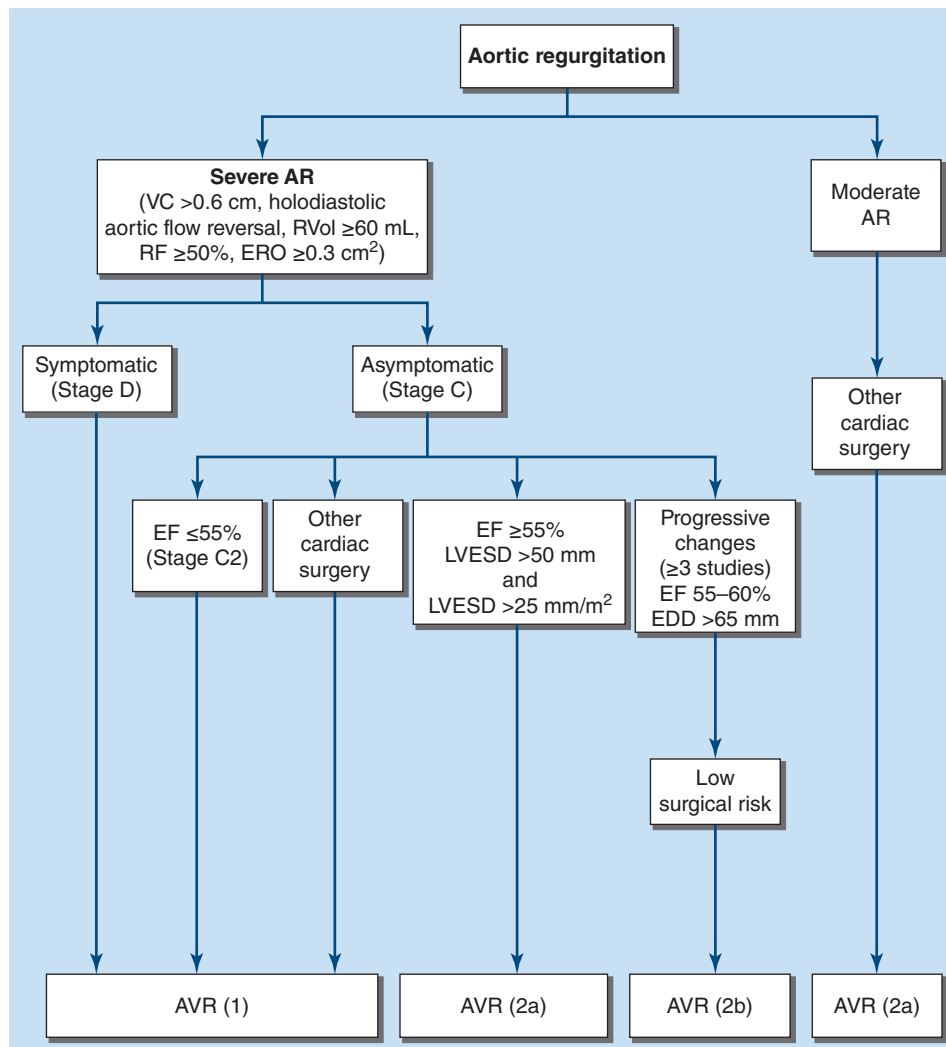


FIGURE 273-2 Management of patients with aortic regurgitation. See legend for Fig. 272-4 for explanation of treatment recommendations (Class I, IIa, and IIb) and disease stages (B, C1, C2, and D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Surgery is indicated for patients with severe AR and symptoms, LV dysfunction, or other indications for operation (e.g., aneurysm disease). Surgery is also reasonable once the LV indexed end-systolic dimension reaches or exceeds 25 mm/m². Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. AR, aortic regurgitation; AVR, aortic valve replacement (valve repair may be appropriate in selected patients); EDD, end-diastolic dimension; EF, ejection fraction; ERO, effective regurgitant orifice; LV, left ventricular; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Reproduced with permission from CM Otto et al: 2020 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2021;143(5):e72.)

(defined as >1 year from onset of symptoms or LV dysfunction), surgical treatment often does not restore normal LV size and function. Therefore, in patients with chronic severe AR, careful clinical follow-up and noninvasive testing with echocardiography at ~6- to 12-month intervals are necessary if operation is to be undertaken at the optimal time, i.e., coincident with or after the onset of LV dysfunction but prior to the development of symptoms. Exercise testing may be helpful to assess effort tolerance more objectively and should be employed whenever questions about symptoms arise. Operation can be deferred as long as the patient both remains asymptomatic and retains normal LV function without severe or progressive chamber dilation.

Aortic valve replacement (AVR) is indicated for the treatment of severe AR in symptomatic patients irrespective of LV function. In general, the operation should be carried out in asymptomatic patients with severe AR and progressive LV dysfunction defined by an LVEF <55% on serial studies, an LV end-systolic dimension >50 mm (>25 mm/m²), or an LV diastolic dimension >65 mm. Smaller dimensions may be appropriate thresholds in individuals of smaller stature or when there is evidence of progressively decreasing LV function or increasing LV size on serial studies and the anticipated risks for surgical morbidity and mortality are low. Two case series

from surgical referral centers have suggested that surgery should be performed at an even lower threshold for LV end-systolic dimension index (≥20 mm/m²), but data from randomized controlled trials are lacking. Abnormal LV GLS (≥ -18%) has been associated with an excess hazard for death in single-center studies. Observational studies using either three-dimensional echocardiography or CMR imaging have also suggested that event-free survival is reduced in asymptomatic patients with an LV end-systolic volume index ≥45 mL/m², compared with patients with an LV end-systolic volume index <45 mL/m². Patients with severe AR without indications for operation should be followed by clinical and echocardiographic examination every 6–12 months. Transcatheter aortic valve implantation (TAVI) is not recommended for patients with severe AR who are surgical candidates. Technical success with TAVI in patients with chronic AR is limited by the degree of aortic annular dilation and the relative paucity of valvular and annular calcium.

Surgical options for management of aortic valve and root disease have expanded considerably over the past decade. AVR with a suitable mechanical or tissue (biological) prosthesis is generally necessary in patients with rheumatic AR and in many patients with other causes of valvular AR. Rarely, when a leaflet has been perforated during IE

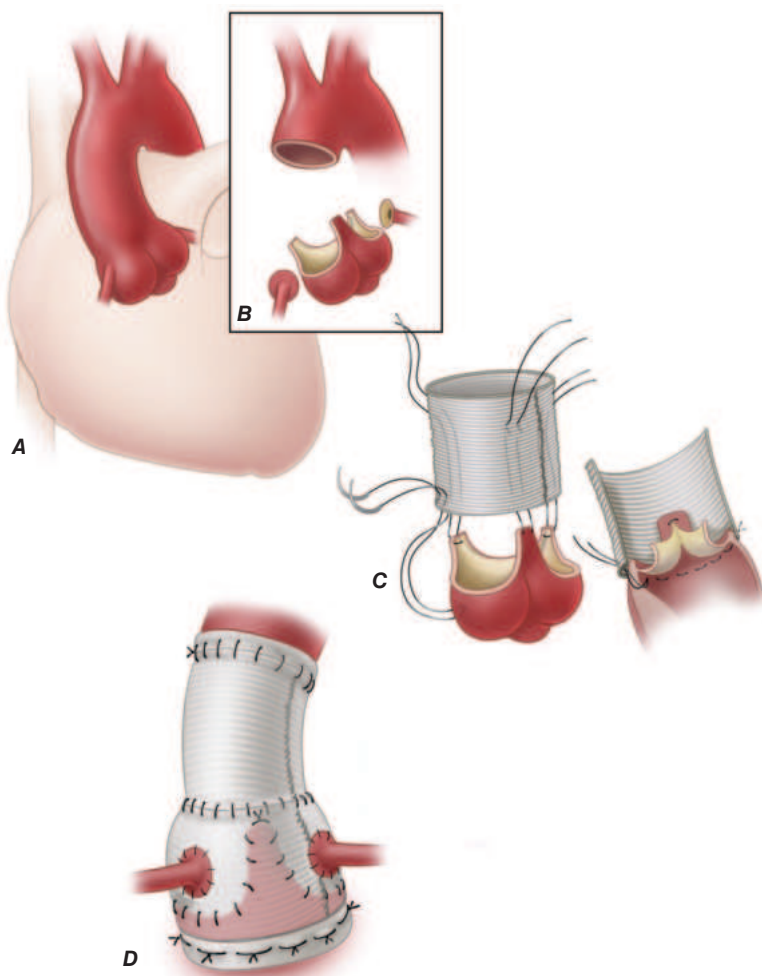


FIGURE 273-3 Valve-sparing aortic root reconstruction (David procedure). Aortic root and proximal ascending aorta (**A**) are resected (**B**) with sinuses of Valsalva and mobilized coronary artery buttons remaining. Subannular sutures (**C**) are placed, commissural posts are drawn up inside the valve, and the annular sutures are passed through the proximal end of the graft. The annular sutures are tied (**D**), the valve is reimplanted inside the graft, aortic continuity is reestablished with another graft of appropriate size, and the coronary buttons are attached to the side of the graft. (From P Steltzer et al [eds]: *Valvular Heart Disease: A Companion to Braunwald's Heart Disease*, 3rd ed, Fig. 12-27, p. 200.)

or torn from its attachments to the aortic annulus by thoracic trauma, primary surgical repair may be possible. When AR is due to aneurysmal dilation of the root or proximal ascending aorta rather than to primary valve involvement, it may be possible to reduce or eliminate the regurgitation by narrowing the annulus or by excising a portion of the aortic root without replacing the valve. Elective, valve-sparing aortic root reconstruction generally involves reimplantation of the valve in a contoured graft with reattachment of the coronary artery buttons into the side of the graft and is best undertaken in specialized surgical centers by experienced operators (Fig. 273-3). Resuspension of the native aortic valve leaflets is possible in ~50% of patients with acute AR in the setting of type A aortic dissection. In other conditions, however, AR can be effectively eliminated only by replacing the aortic valve, as well as the dilated or aneurysmal ascending aorta responsible for the regurgitation, often using a composite prosthetic valve-graft conduit. Pure AR is not by itself a contraindication to the Ross procedure, although the presence of aortic annular dilation and/or an associated aortopathy would eliminate this option.

As is true in patients with other valvular heart disease, both operative and late mortality risks are largely dependent on the stage of the disease and myocardial function at the time of operation. The overall operative mortality rate for isolated AVR performed for pure AR is ~1–2%. The mortality risk doubles when aortic surgery is added to the operation. Patients with AR, marked cardiac enlargement, and established LV dysfunction experience an operative mortality rate of ~5–10% and a late mortality rate of ~3–5% per

year due to LV failure despite a technically satisfactory operation. Nonetheless, because of the very poor prognosis with medical management, even patients with advanced LV systolic dysfunction should be considered for operation.

Patients with acute severe AR require prompt (24–48 h) surgical treatment, which may be lifesaving.

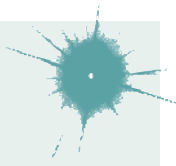
■ FURTHER READING

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274

Mitral Stenosis

Patrick T. O'Gara, Joseph Loscalzo



The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in [Chaps. 44 and 246](#); of electrocardiography (ECG) in [Chap. 247](#); of echocardiography and other noninvasive imaging techniques in [Chap. 248](#); and of cardiac catheterization and angiography in [Chap. 249](#).

MITRAL STENOSIS

■ ETIOLOGY AND PATHOLOGY

Rheumatic fever is the leading cause of mitral stenosis (MS) ([Table 274-1](#); see also [Chap. 371](#)). Other less common etiologies of obstruction to left ventricular inflow include congenital mitral valve stenosis, cor triatriatum, mitral annular calcification with extension onto the leaflets, systemic lupus erythematosus, rheumatoid arthritis, left atrial myxoma, and infective endocarditis with large vegetations. Pure or predominant MS occurs in ~40% of all patients with rheumatic heart disease and a history of rheumatic fever ([Chap. 371](#)). In other patients with rheumatic heart disease, lesser degrees of MS may accompany mitral regurgitation (MR) and aortic valve disease. With reductions in the incidence of acute rheumatic fever, particularly in temperate climates and middle- to high-income countries, the incidence of MS has declined considerably over the past several decades. However, it remains a major problem in low-income countries, especially in sub-Saharan Africa, India, Southeast Asia, and Oceania ([Chap. 272](#)).

In rheumatic MS, chronic inflammation leads to diffuse thickening of the valve leaflets with formation of fibrous tissue often with calcific deposits. The mitral commissures fuse, the chordae tendineae fuse and shorten, the valvular cusps become rigid, and the pathologic process eventually leads to narrowing at the apex of the funnel-shaped (“fish-mouth”) valve. Although the initial insult to the mitral valve is rheumatic, later changes may be exacerbated by inflammation, fibrosis, and trauma due to altered flow patterns. Calcification of the stenotic mitral valve immobilizes the leaflets and narrows the orifice further. Thrombus formation and arterial embolization may arise from the calcific valve itself, but in patients with atrial fibrillation (AF), thrombi arise more frequently from the dilated left atrium (LA), particularly from within the LA appendage.

■ PATHOPHYSIOLOGY

In normal adults, the area of the mitral valve orifice is 4–6 cm². In the presence of significant obstruction, i.e., when the orifice area is reduced to <2 cm², blood can flow from the LA to the left ventricle (LV) only if propelled by an abnormally elevated left atrioventricular pressure gradient, the hemodynamic hallmark of MS. When the mitral valve opening is reduced to <1.5 cm², referred to as “severe” MS, an LA pressure of ~25 mmHg is required to maintain a normal cardiac output (CO). The elevated pulmonary venous and pulmonary arterial (PA) wedge pressures reduce pulmonary compliance, contributing to exertional dyspnea. The first bouts of dyspnea are usually precipitated

by clinical events that increase the rate of blood flow across the mitral orifice, resulting in further elevation of the LA pressure (see below).

To assess the severity of obstruction hemodynamically, both the transvalvular pressure gradient and the flow rate must be measured ([Chap. 249](#)). The latter depends not only on the CO but on the heart rate, as well. An increase in heart rate shortens diastole proportionately more than systole and diminishes the time available for flow across the mitral valve. Therefore, at any given level of CO, tachycardia, including that associated with rapid AF, augments the transvalvular pressure gradient and elevates further the LA pressure. Similar considerations apply to the pathophysiology of tricuspid stenosis (TS).

The LV diastolic pressure and ejection fraction (EF) are normal in isolated MS. In MS and sinus rhythm, the elevated LA and PA wedge pressures exhibit a prominent atrial contraction pattern (*a* wave) and a gradual pressure decline after the *v* wave and mitral valve opening (*y* descent). In severe MS and whenever pulmonary vascular resistance is significantly increased, the PA pressure (PAP) is elevated at rest and rises further during exercise, often causing secondary elevations of right ventricular (RV) end-diastolic pressure and volume.

Cardiac Output In patients with severe MS (mitral valve orifice 1–1.5 cm²), the CO is normal or almost so at rest, but rises subnormally during exertion. In patients with very severe MS (valve area <1 cm²), particularly those in whom pulmonary vascular resistance is markedly elevated, the CO is subnormal at rest and may fail to rise or may even decline during activity.

Pulmonary Hypertension The clinical and hemodynamic features of MS are influenced importantly by the level of the PAP. Pulmonary hypertension results from (1) passive backward transmission of the elevated LA pressure; (2) pulmonary arteriolar constriction (the so-called “second stenosis”), which presumably is triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension); (3) interstitial edema in the walls of the small pulmonary vessels; and (4) at end stage, organic obliterative changes in the pulmonary vascular bed. Severe pulmonary hypertension results in RV enlargement, secondary tricuspid regurgitation (TR), and pulmonic regurgitation (PR), as well as right-sided heart failure.

■ SYMPTOMS

In temperate climates, the latent period between the initial attack of rheumatic carditis (in the increasingly rare circumstances in which a history of one can be elicited) and the development of symptoms due to MS is generally about two decades; most patients begin to experience disability in the fourth decade of life. Studies carried out before the development of surgical mitral valvotomy revealed that once a patient with MS became seriously symptomatic, the disease progressed inexorably to death within 2–5 years.

In patients whose mitral orifices are large enough to accommodate a normal blood flow with only mild elevations of LA pressure, marked elevations of this pressure leading to dyspnea and cough may be precipitated by sudden changes in the heart rate, volume status, or CO, as, for example, with severe exertion, excitement, fever, severe anemia, paroxysmal AF and other tachycardias, sexual intercourse, pregnancy, and thyrotoxicosis. As MS progresses, lesser degrees of stress precipitate dyspnea, the patient becomes limited in daily activities, and orthopnea and paroxysmal nocturnal dyspnea develop. The development of persistent AF often marks a turning point in the patient's course and is generally associated with acceleration of the rate at which symptoms progress. *Hemoptysis* ([Chap. 41](#)) results from rupture of pulmonary-bronchial venous connections secondary to pulmonary venous hypertension. It occurs most frequently in patients who have elevated LA pressures without markedly elevated pulmonary vascular resistances and is rarely fatal. *Recurrent pulmonary emboli* ([Chap. 290](#)), sometimes with infarction, are an important cause of morbidity and mortality late in the course of MS and often arise from right atrial mural thrombus. *Pulmonary infections*, i.e., bronchitis, bronchopneumonia, and lobar pneumonia, commonly complicate untreated MS, especially during the winter months. In patients with significant left atrial enlargement,

TABLE 274-1 Major Causes of Mitral Stenosis

Etiologies

Rheumatic fever
Congenital (parachute valve, cor triatriatum)
Severe mitral annular calcification with leaflet involvement
SLE, RA
Myxoma
IE with large vegetations

Abbreviations: IE, infective endocarditis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

cardiovascular syndrome (Ortner's syndrome) may develop with hoarseness secondary to left recurrent laryngeal nerve compression.

Pulmonary Changes In addition to the aforementioned changes in the pulmonary vascular bed, fibrous thickening of the walls of the alveoli and pulmonary capillaries occurs commonly in MS. The vital capacity, total lung capacity, maximal breathing capacity, and oxygen uptake per unit of ventilation are reduced (Chap. 296). Pulmonary compliance falls further as pulmonary capillary pressure rises during exercise.

Thrombi and Emboli *Thrombi* may form in the left atria, particularly within the enlarged atrial appendages of patients with MS. Systemic embolization, the incidence of which is 10–20%, occurs more frequently in patients with AF, in patients >65 years of age, and in those with a reduced CO. However, systemic embolization may be the presenting feature in otherwise asymptomatic patients with only mild MS.

■ PHYSICAL FINDINGS (See also Chaps. 44 and 246).

Inspection and Palpation In patients with severe MS, there may be a malar flush with pinched and blue facies. In patients with sinus rhythm and severe pulmonary hypertension or associated TS, the jugular venous pulse reveals prominent *a* waves due to vigorous right atrial systole. The systemic arterial pressure is usually normal or slightly low. A parasternal lift signifies an enlarged RV. A diastolic thrill may very rarely be present at the cardiac apex, with the patient in the left lateral recumbent position.

Auscultation The first heart sound (S_1) is usually accentuated in the early stages of the disease and slightly delayed. The pulmonic component of the second heart sound (P_2) also is often accentuated with elevated PAPs, and the two components of the second heart sound (S_2) are closely split. The opening snap (OS) of the mitral valve is most readily audible in expiration at, or just medial to, the cardiac apex. This sound generally follows the sound of aortic valve closure (A_2) by 0.05–0.12 s. The time interval between A_2 and OS varies inversely with the severity of the MS. The OS is followed by a low-pitched, rumbling, diastolic murmur, heard best at the apex with the patient in the left lateral recumbent position (see Fig. 246-5); it is accentuated by mild exercise (e.g., a few rapid sit-ups) carried out just before auscultation. In general, the duration of this murmur correlates with the severity of the stenosis in patients with preserved CO. In patients with sinus rhythm, the murmur often reappears or becomes louder during atrial systole (presystolic accentuation). Soft, grade I or II/VI systolic murmurs may be heard at or medial to the apex and may signify mixed mitral valve disease with regurgitation. Hepatomegaly, ankle edema, ascites, and pleural effusion, particularly in the right pleural cavity, may occur in patients with MS and RV failure.

Associated Lesions With severe pulmonary hypertension, a pansystolic murmur produced by functional TR may be audible along the left sternal border. This murmur is usually louder during inspiration and diminishes during forced expiration (Carvallo's sign). When the CO is markedly reduced in MS, the typical auscultatory findings, including the diastolic rumbling murmur, may not be detectable (silent MS), but they may reappear as compensation is restored. The *Graham Steell murmur* of PR, a high-pitched, diastolic, decrescendo blowing murmur along the left sternal border, results from dilation of the pulmonary valve ring and occurs in patients with mitral valve disease and severe pulmonary hypertension. This murmur may be indistinguishable from the more common murmur produced by aortic regurgitation (AR), although it may increase in intensity with inspiration and is accompanied by a loud and often palpable P_2 .

■ LABORATORY EXAMINATION

ECG In MS and sinus rhythm, the P wave usually suggests LA enlargement (see Fig. 247-8). It may become tall and peaked in lead II and upright in lead V_1 when severe pulmonary hypertension or TS

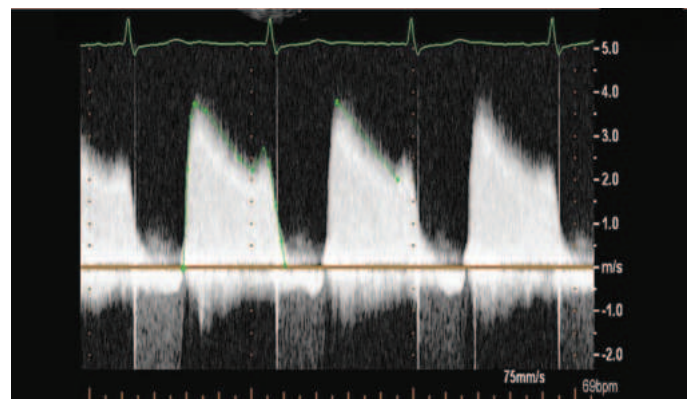


FIGURE 274-1 Continuous wave Doppler interrogation of transmitral valve velocities in a patient with severe rheumatic mitral stenosis. Electrocardiogram on top. Vertical scale in meters/second. Horizontal scale in seconds at sweep speed of 75 mm/se. Velocity is converted to pressure using the Bernoulli equation. In this example, the mean mitral valve gradient (area under the green tracing) is calculated to 38 mmHg and mitral valve area to 0.7 cm^2 .

complicates MS and right atrial (RA) enlargement develops. The QRS complex is usually normal. However, with severe pulmonary hypertension, right axis deviation and RV hypertrophy are often present.

Echocardiogram (See also Chap. 248) Transthoracic echocardiography (TTE) with color flow and spectral Doppler imaging provides critical information, including measurements of mitral inflow velocity during early (E wave) and late (A wave in patients in sinus rhythm) diastolic filling, estimates of the transvalvular peak and mean gradients and mitral orifice area (Fig. 274-1), the presence and severity of any associated MR, the extent of leaflet calcification and restriction, the degree of distortion of the subvalvular apparatus, and the anatomic suitability for percutaneous mitral balloon commissurotomy (PMBC; see below). In addition, TTE provides an assessment of LV and RV function, chamber sizes, an estimation of the PA systolic pressure based on the tricuspid regurgitant jet velocity, and an indication of the presence and severity of any associated valvular lesions, such as aortic stenosis (AS) and/or regurgitation. Transesophageal echocardiography (TEE) provides superior images and should be used when TTE is inadequate for guiding management decisions. TEE is especially indicated to exclude the presence of LA thrombus prior to PMBC. The performance of TTE with exercise to evaluate the mean mitral diastolic gradient, PAPs, and RV function can be very helpful in the evaluation of patients with MS when there is a discrepancy between the clinical findings and the resting hemodynamics.

Chest X-Ray The earliest changes are straightening of the upper left border of the cardiac silhouette, prominence of the main PAs, dilation of the upper lobe pulmonary veins, and posterior displacement of the esophagus by an enlarged LA. Kerley B lines are fine, dense, opaque, horizontal lines that are most prominent in the lower and mid-lung fields that result from distention of interlobular septae and lymphatics with edema when the resting mean LA pressure exceeds ~20 mmHg.

■ DIFFERENTIAL DIAGNOSIS

Like MS, significant MR may also be associated with a prominent diastolic murmur at the apex due to increased antegrade transmitral flow, but in patients with isolated MR, this diastolic murmur commences slightly later than in patients with MS, and there is often clear-cut evidence of LV enlargement. An OS and increased P_2 are absent, and S_1 is soft or absent. An apical pansystolic murmur of at least grade III/VI intensity as well as an S_3 suggests significant MR. Similarly, the apical mid-diastolic murmur associated with severe AR (*Austin Flint murmur*) may be mistaken for MS but can be differentiated from it because it is not intensified in pre-systole and becomes softer with administration of amyl nitrite or other arterial vasodilators. TS, which occurs rarely in the absence of MS, may mask many of the clinical features of MS or be clinically silent; when present, the diastolic murmur of

2050 TS increases with inspiration and the y descent in the jugular venous pulse is delayed.

Atrial septal defect (Chap. 280) may be mistaken for MS; in both conditions, there is often clinical, ECG, and chest x-ray evidence of RV enlargement and accentuation of pulmonary vascularity. However, the absence of LA enlargement and of Kerley B lines and the demonstration of fixed splitting of S₂ with a grade II or III mid-systolic murmur at the mid to upper left sternal border all favor atrial septal defect over MS. Atrial septal defects with large left-to-right shunts may result in functional TS because of the enhanced diastolic flow. An incomplete right bundle branch block pattern on ECG is often present.

Left atrial myxoma (Chap. 282) may obstruct LA emptying, causing dyspnea, a diastolic murmur, and hemodynamic changes resembling those of MS. However, patients with an LA myxoma often have features suggestive of a systemic disease, such as weight loss, fever, anemia, systemic emboli, and elevated serum IgG and interleukin 6 (IL-6) concentrations. The auscultatory findings may change markedly with body position. The diagnosis can be established by the demonstration of a characteristic echo-producing mass in the LA with TTE.

■ CARDIAC CATHETERIZATION

Left and right heart catheterization can be useful when there is a discrepancy between the clinical and noninvasive findings, including those from TEE and exercise echocardiographic testing when appropriate. Catheterization can also be helpful in assessing associated lesions, such as AS and AR, and in patients with recurring or worsening symptoms late after mitral valve intervention. Computed tomographic coronary angiography is increasingly used to screen preoperatively for

the presence of coronary artery disease in appropriate patients prior to heart valve surgery or transcatheter treatment.

TREATMENT

Mitral Stenosis (Fig. 274-2)

Penicillin prophylaxis of group A β -hemolytic streptococcal infections (Chap. 371) for secondary prevention of rheumatic fever is important for at-risk patients with rheumatic MS. Recommendations for infective endocarditis prophylaxis are similar to those for other valve lesions and are restricted to patients at high risk for complications from infection, including patients with a history of endocarditis. In symptomatic patients, some improvement usually occurs with restriction of sodium intake and small doses of oral diuretics. Beta blockers, nondihydropyridine calcium channel blockers (e.g., verapamil or diltiazem), and digitalis glycosides are useful in slowing the ventricular rate of patients with AF. Vitamin K antagonist therapy (such as warfarin) targeted to an international normalized ratio (INR) of 2–3 should be administered indefinitely to patients with MS who have AF, a history of thromboembolism, or demonstrated LA thrombus. The routine use of a vitamin K antagonist in patients in sinus rhythm with LA enlargement (maximal dimension >5.5 cm) with or without spontaneous echo contrast is more controversial. In a randomized trial of patients with rheumatic MS and AF, there was a significantly higher incidence of death among patients treated with rivaroxaban than with vitamin K antagonist therapy. A vitamin K antagonist is

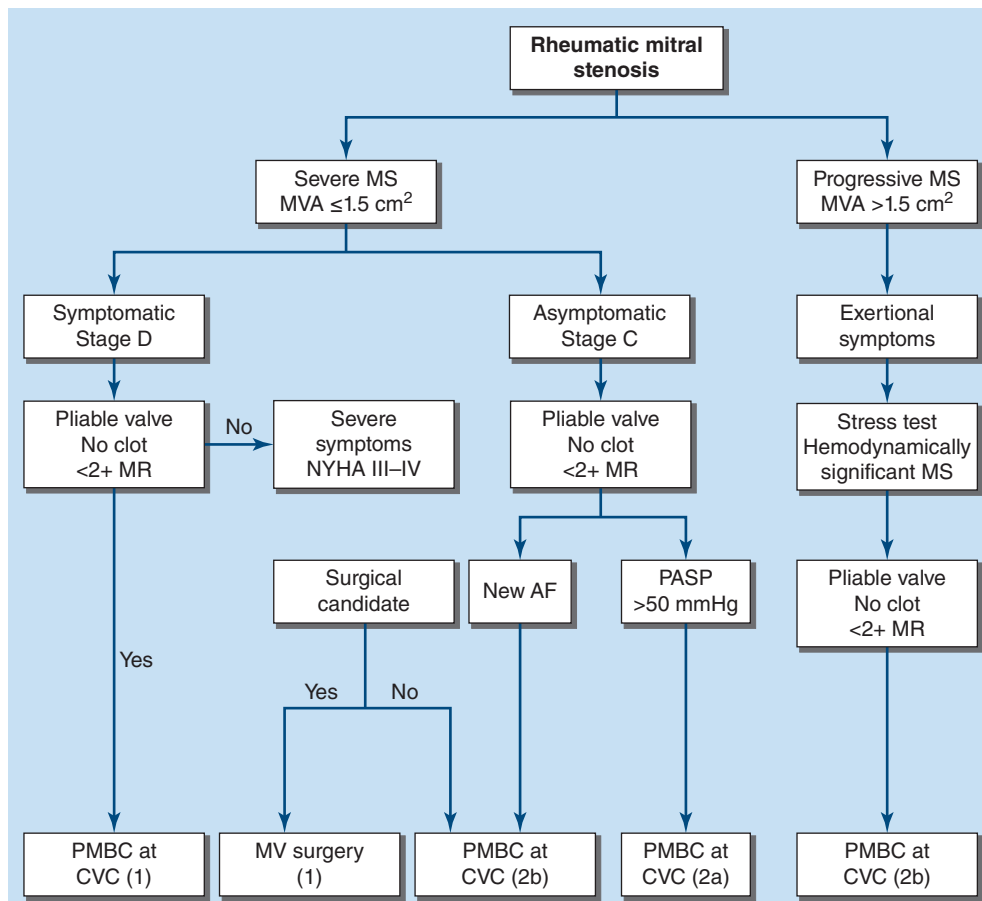


FIGURE 274-2 Management of rheumatic mitral stenosis. See legend for Fig. 272-4 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; CVC, comprehensive valve center; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; PMBC, percutaneous mitral balloon commissurotomy. (Reproduced with permission from CM Otto et al: ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 143:e72, 2021.)

recommended to reduce the risk for stroke or systemic embolism in at-risk patients with rheumatic MS.

If AF is of relatively recent onset in a patient whose MS is not severe enough to warrant PMBC or surgical intervention, reversion to sinus rhythm pharmacologically or by means of electrical countershock is indicated. Usually, cardioversion should be undertaken after the patient has had at least 3 consecutive weeks of anticoagulant treatment to a therapeutic INR. If cardioversion is indicated more urgently, then intravenous heparin should be provided and TEE performed to exclude the presence of LA thrombus before the procedure. Conversion to sinus rhythm is rarely successful or sustained in patients with severe MS, particularly those in whom the LA is significantly enlarged or in whom AF has been present for >1 year, conditions that favor the development of an LA myopathy.

MITRAL COMMISSUROTOMY

Unless there is a contraindication, mitral commissurotomy is indicated in symptomatic (New York Heart Association [NYHA] functional class II–IV) patients with isolated severe MS, whose effective orifice (valve area) is $<1 \text{ cm}^2/\text{m}^2$ body surface area or $<1.5 \text{ cm}^2$ in normal-sized adults. Mitral commissurotomy can be carried out either percutaneously or surgically. In PMBC (Figs. 274-3 and 274-4), a catheter is directed into the LA after transseptal puncture, and a single balloon is directed across the valve and inflated in the valvular orifice. Ideal patients have relatively pliable leaflets with little or no commissural calcium. In addition, the subvalvular structures should not be significantly scarred or thickened, and there should be no LA thrombus. Any associated MR should be of $\leq 2+/4+$ severity. The short- and long-term results of this procedure in appropriate patients are similar to those of surgical commissurotomy, but with less morbidity and a lower periprocedural mortality rate. Event-free survival in younger (<45 years) patients with pliable valves is excellent, with rates as high as 80–90% over 3–7 years. Therefore, PMBC is the procedure of choice for such patients when it can be performed by a skilled operator in a high-volume center.

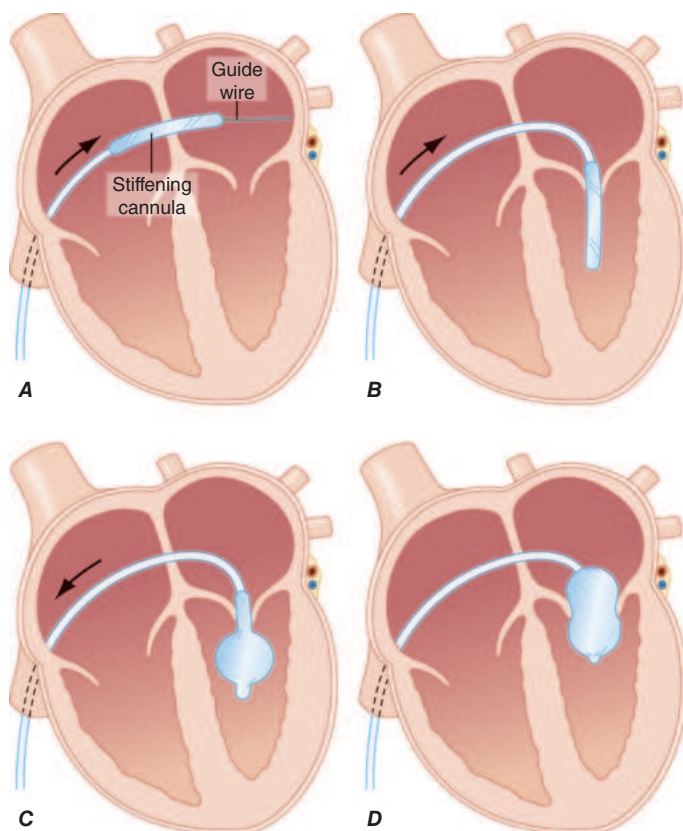


FIGURE 274-3 Inoue balloon technique for percutaneous mitral balloon commissurotomy. **A.** After transseptal puncture, the deflated balloon catheter is advanced across the interatrial septum, then across the mitral valve and into the left ventricle. **B–D.** The balloon is inflated stepwise within the mitral orifice.

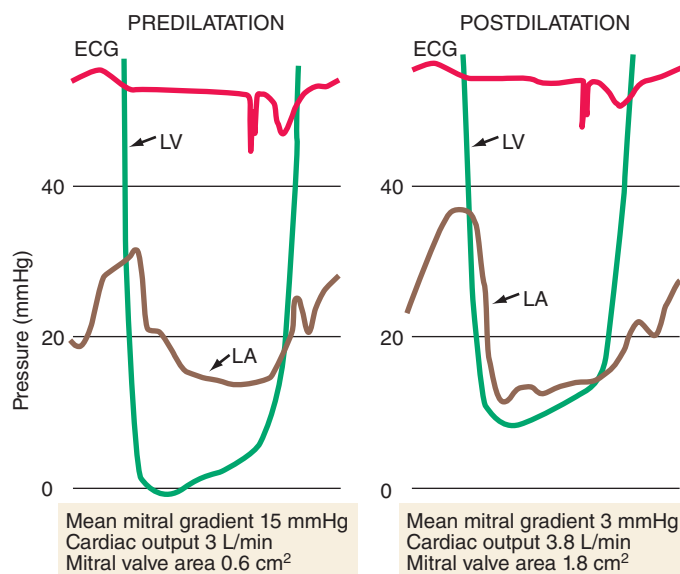


FIGURE 274-4 Simultaneous left atrial (LA) and left ventricular (LV) pressure before and after percutaneous mitral balloon commissurotomy (PMBC) in a patient with severe mitral stenosis. ECG, electrocardiogram. (Courtesy of Raymond G. McKay, MD.)

TTE is helpful in identifying patients for the percutaneous procedure; TEE is performed routinely to exclude LA thrombus and to assess the degree of MR at the time of the scheduled procedure. An “echo score” has been developed to help guide decision-making. The score accounts for the degree of leaflet thickening, calcification, and mobility, and for the extent of subvalvular thickening. A lower score predicts a higher likelihood of successful PMBC.

In patients in whom PMBC is not possible or unsuccessful, or in many patients with restenosis after previous surgery, an “open” surgical commissurotomy using cardiopulmonary bypass is necessary. In addition to opening the valve commissures, it is important to loosen any subvalvular fusion of papillary muscles and chordae tendineae; to remove large deposits of calcium, thereby improving valvular function; and to remove atrial thrombi. The perioperative mortality rate for this type of mitral valve repair procedure is ~2%.

Successful commissurotomy is defined by a 50% reduction in the mean mitral valve gradient and a doubling of the mitral valve area. Successful commissurotomy, whether balloon or surgical, usually results in striking symptomatic and hemodynamic improvement and prolongs survival. However, there is no evidence that the procedure improves the prognosis of patients with slight or no functional impairment. Therefore, unless recurrent systemic embolization or severe pulmonary hypertension has occurred (PA systolic pressures >50 mmHg at rest or >60 mmHg with exercise), commissurotomy is *not* recommended for patients who are asymptomatic and/or who have mild or moderate stenosis (mitral valve area $>1.5 \text{ cm}^2$). When there is little symptomatic improvement after commissurotomy, it is likely that the procedure was ineffective, that it induced MR, or that associated valvular or myocardial disease was present. About half of all patients undergoing surgical mitral commissurotomy require reoperation by 10 years. In the pregnant patient with MS, commissurotomy should be carried out if pulmonary congestion occurs despite intensive medical treatment. PMBC is the preferred strategy in this setting and is performed with TEE and no or minimal x-ray exposure.

Mitral valve replacement (MVR) is necessary in patients with MS and significant associated MR, those in whom the valve has been severely distorted by previous transcatheter or operative manipulation, or those in whom the surgeon does not find it possible to improve valve function significantly with commissurotomy. MVR is now routinely performed with preservation of the chordal attachments to optimize LV functional recovery. Perioperative mortality rates with MVR vary with age, LV function, the presence of CAD, and associated comorbidities. They average 2–5% overall but

are lower in young patients and may be twice as high in patients >65 years of age with significant comorbidities. Because there are also long-term complications of valve replacement, patients in whom preoperative evaluation suggests the possibility that MVR may be required should be operated on only if they have severe MS—i.e., an orifice area $\leq 1.5\text{ cm}^2$ —and are in NYHA class III, i.e., symptomatic with ordinary activity despite optimal medical therapy. The overall 10-year survival of surgical survivors is ~70%. Long-term prognosis is worse in patients >65 years of age and those with marked disability and marked depression of the CO preoperatively. Pulmonary hypertension and RV dysfunction are additional risk factors for poor outcome.

FURTHER READING

CONNOLLY SJ et al: Rivaroxaban in rheumatic heart disease-associated atrial fibrillation. *N Engl J Med* 387:978, 2022.
NISHIMURA RA et al: Mitral valve disease: Current management and future challenges. *Lancet* 387:1324, 2016.
OTTO CM et al: 2020 ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 143:e72, 2021.

275

Mitral Regurgitation

Patrick T. O’Gara, Joseph Loscalzo



The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in [Chaps. 44 and 246](#); of electrocardiography (ECG) in [Chap. 247](#); of echocardiography and other noninvasive imaging techniques in [Chap. 248](#); and of cardiac catheterization and angiography in [Chap. 249](#).

ETIOLOGY

Mitral regurgitation (MR) may result from an abnormality or disease process that affects any one or more of the five functional components of the mitral valve apparatus (leaflets, annulus, chordae tendineae, papillary muscles, and subjacent myocardium) ([Table 275-1](#)). Acute MR can occur in the setting of acute myocardial infarction (MI) with papillary muscle rupture ([Chap. 286](#)), following blunt chest wall trauma, or during the course of infective endocarditis (IE) owing to leaflet perforation or destruction. With acute MI, the posteromedial papillary muscle is involved much more frequently than the anterolateral papillary muscle because of its singular blood supply. Transient, acute MR can occur during periods of active ischemia and bouts of angina pectoris. Rupture of chordae tendineae can result in “acute-on-chronic MR” in patients with myxomatous degeneration of the valve apparatus. Chronic MR can result from several disease processes ([Table 275-1](#)). Distinction should be drawn between primary (degenerative) MR, in which the leaflets and/or chordae tendineae are primarily responsible for abnormal valve function, and secondary (functional) MR, in which the leaflets and chordae tendineae are usually normal but the regurgitation is caused by left ventricular (LV) and/or left atrial remodeling, annular dilation, papillary muscle displacement, dyssynchrony, leaflet tethering, or their combination. Patient assessment, treatment approach, and long-term prognosis differ significantly between primary and secondary MR. Mitral valve prolapse (MVP) is discussed more extensively in [Chap. 276](#). The rheumatic process produces rigidity, deformity, and retraction of the valve cusps and commissural fusion, as well as shortening, contraction, and fusion of the chordae tendineae. MR can persist after resolution of the acute phase

TABLE 275-1 Major Causes of Mitral Regurgitation (MR)

Etiologies
Acute
IE
Papillary muscle rupture (post-MI)
Chordal rupture/leaflet flail (MVP, IE)
Blunt trauma
Chronic
Primary (affecting leaflets, chordae)
Myxomatous (MVP, Barlow’s, <i>forme fruste</i>)
Rheumatic fever
IE (healed)
Congenital (cleft, AV canal)
Radiation
Secondary (leaflets, chordae are “innocent bystanders”)
Ischemic cardiomyopathy
Dilated cardiomyopathy
HOCM (with SAM)
AF with LA enlargement and annular dilation (atrial functional MR)
Mitral annular calcification^a

^aMitral annular calcification may include elements of both primary and secondary MR (mixed) as the disease process may encroach on the leaflets, impair the normal sphincteric function of the annulus, or both. There are additional examples of “mixed” secondary MR such as the coexistence of MVP with an ischemic cardiomyopathy.
Abbreviations: AF, atrial fibrillation; AV, atrioventricular; HOCM, hypertrophic obstructive cardiomyopathy; IE, infective endocarditis; LA, left atrial; LV, left ventricular; MI, myocardial infarction; MVP, mitral valve prolapse; SAM, systolic anterior motion.

of infection and inflammation. MR may occur as a congenital anomaly ([Chap. 280](#)), most commonly as a defect of the endocardial cushions (atrioventricular cushion defects). A cleft anterior mitral valve leaflet accompanies ostium primum atrial septal defect. Radiation can result in leaflet thickening, retraction, and calcification, often in association with annular and chordal involvement and some degree of mitral stenosis. Chronic MR occurs frequently after prior MI(s) associated with changes in LV size, shape, and function. Similar mechanisms of annular dilation and ventricular remodeling contribute to the MR that occurs among patients with nonischemic forms of dilated cardiomyopathy once the LV end-diastolic dimension reaches 6 cm. The MR associated with hypertrophic obstructive cardiomyopathy (HOCM) is usually dynamic in nature and dependent on systolic anterior motion of the anterior mitral valve leaflet into a narrowed LV outflow tract. Patients with chronic persistent atrial fibrillation (AF) may develop atrial remodeling and annular dilation with inadequate leaflet lengthening and MR (atrial functional MR). Secondary MR due to LV remodeling is more frequently encountered in the community than secondary MR that occurs in association with AF and annular dilation. Annular calcification can result in MR when it encroaches on the leaflets or results in decreased sphincteric function, is especially prevalent among patients with advanced renal disease, and is commonly observed in women >65 years of age with hypertension and diabetes mellitus. Irrespective of cause, chronic severe MR is often progressive because enlargement of the left atrium (LA) places tension on the posterior mitral leaflet, pulling it further away from the mitral orifice and thereby aggravating the valvular dysfunction. Similarly, LV dilation increases the regurgitation, which, in turn, enlarges the LA and LV further, resulting in a vicious cycle; hence the aphorism, “MR begets MR.”

PATHOPHYSIOLOGY

The resistance to LV emptying (LV afterload) is reduced in patients with MR. As a consequence, the LV is decompressed into the LA during ejection, and with the reduction in LV size during systole, there is a rapid decline in LV tension. The initial compensation to MR is more complete LV emptying. However, LV volume increases progressively with time as the severity of the regurgitation increases and as LV contractile function deteriorates. This increase in LV volume is often accompanied

by a reduced forward cardiac output (CO). LV compliance is often increased, and thus, LV diastolic pressure does not increase until late in the course. The regurgitant volume varies directly with the LV systolic pressure and the size of the regurgitant orifice; the latter, in turn, is influenced by the extent of LV and mitral annular dilation, as well as by leaflet morphology. Because ejection fraction (EF) rises in severe MR in the presence of normal LV function, even a modest reduction in this parameter (<60%) reflects significant contractile dysfunction.

During early diastole, as the distended LA empties, there is a particularly rapid γ descent in the absence of accompanying MS. A brief, early diastolic LA-LV pressure gradient (often generating a rapid filling sound [S_3] and mid-diastolic murmur masquerading as MS) may occur in patients with pure, severe MR as a result of the very rapid flow of blood across a normal-sized mitral orifice.

Measurements of LV ejection fraction (LVEF), CO, pulmonary arterial (PA) systolic pressure, regurgitant volume, regurgitant fraction (RF), and the effective regurgitant orifice area can be obtained during a careful Doppler echocardiographic examination. These measurements can also be obtained accurately with cardiac magnetic resonance (CMR) imaging, although this technology is not widely available. Left and right heart catheterization with contrast ventriculography is used less frequently. Chronic, severe MR is defined by a regurgitant volume ≥ 60 mL/beat, RF $\geq 50\%$, and effective regurgitant orifice area ≥ 0.40 cm². In patients with secondary MR, in whom the severity of MR can be underappreciated using echocardiographic/Doppler techniques, lesser degrees of regurgitation may carry relatively greater prognostic weight. The adverse prognosis in secondary MR related to adverse LV remodeling is intimately related to the degree of myocardial dysfunction.

LA Compliance In acute severe MR, the regurgitant volume is delivered into a normal-sized LA having normal or reduced compliance. As a result, LA pressures rise markedly for any increase in LA volume. The v wave in the LA pressure pulse is usually prominent, LA and pulmonary venous pressures are markedly elevated, and pulmonary edema is common. Because of the rapid rise in LA pressures during ventricular systole, the murmur of acute MR is early in timing and decrescendo in configuration ending well before S_2 , as a reflection of the progressive diminution in the LV-LA pressure gradient. LV systolic function in acute MR may be normal, hyperdynamic, or reduced, depending on the clinical context.

Patients with chronic severe MR, on the other hand, develop marked LA enlargement and increased LA compliance with little if any increase in LA and pulmonary venous pressures for any increase in LA volume. The LA v wave is relatively less prominent. The murmur of chronic MR is classically holosystolic in timing and plateau in configuration, as a reflection of the near-constant LV-LA pressure gradient. These patients usually complain of severe fatigue and exhaustion secondary to a low forward CO, whereas symptoms resulting from pulmonary congestion are less prominent initially; AF is almost invariably present once the LA dilates significantly.

■ SYMPTOMS

Patients with chronic mild-to-moderate, isolated MR are usually asymptomatic. This form of LV volume overload is well tolerated. Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic severe MR. Palpitations are common and may signify the onset of AF. Late-onset right-sided heart failure, with painful hepatic congestion, ankle edema, distended neck veins, ascites, and secondary tricuspid regurgitation (TR), occurs in patients with MR who have associated pulmonary vascular disease and pulmonary hypertension. Acute pulmonary edema is common in patients with acute severe MR.

■ PHYSICAL FINDINGS

In patients with chronic severe MR, the arterial pressure is usually normal, although the carotid arterial pulse may show a sharp, low-volume upstroke owing to the reduced forward CO. A systolic thrill is often palpable at the cardiac apex, the LV is hyperdynamic with a brisk systolic impulse and a palpable rapid-filling wave (S_3), and the apex beat is often displaced laterally.

In patients with acute severe MR, the arterial pressure may be reduced with a narrow pulse pressure, the jugular venous pressure and waveforms may be normal or increased and exaggerated, the apical impulse is not displaced, and signs of pulmonary congestion are prominent.

Auscultation S_1 is generally absent, soft, or buried in the holosystolic murmur of chronic, severe MR. In patients with severe MR, the aortic valve may close prematurely (due to the reduced forward cardiac output), resulting in wide but physiologic splitting of S_2 . A low-pitched S_3 occurring 0.12–0.17 s after the aortic valve closure sound, i.e., at the completion of the rapid-filling phase of the LV, is believed to be caused by the sudden tensing of the papillary muscles, chordae tendineae, and valve leaflets. It may be followed by a short, rumbling, mid-diastolic murmur, even in the absence of structural MS. In patients with ischemic or dilated cardiomyopathy, however, a third sound (S_3) may also signify ventricular dysfunction. A fourth heart sound is often audible in patients with acute severe MR who are in sinus rhythm. A presystolic murmur is not ordinarily heard with isolated MR.

A systolic murmur of at least grade III/VI intensity is the most characteristic auscultatory finding in chronic severe MR. It is usually holosystolic (see Fig. 246-5A), but as previously noted, it is decrescendo and ceases in mid-to-late systole in patients with acute severe MR. The systolic murmur of chronic MR is usually most prominent at the apex and radiates to the axilla. However, in patients with ruptured chordae tendineae or primary involvement of the posterior mitral leaflet with prolapse or flail, the regurgitant jet is eccentric, directed anteriorly, and strikes the LA wall adjacent to the aortic root. In this situation, the systolic murmur is transmitted to the base of the heart and, therefore, may be confused with the murmur of AS. The murmur associated with anterior leaflet prolapse or flail is directed to the axilla. In patients with ruptured chordae tendineae, the systolic murmur may have a cooing or “seagull” quality, whereas a flail leaflet may produce a murmur with a musical quality. The systolic murmur of chronic MR not due to MVP is intensified by isometric exercise (handgrip) but is reduced during the strain phase of the Valsalva maneuver because of the associated decrease in LV preload.

■ LABORATORY EXAMINATION

ECG In patients with sinus rhythm, there is evidence of LA enlargement, but right atrial (RA) enlargement also may be present when pulmonary hypertension is significant and affects right ventricular function and size. Chronic severe MR is frequently associated with AF. In many patients, there is no clear-cut ECG evidence of enlargement of either ventricle. In others, the signs of eccentric LV hypertrophy are present.

Echocardiogram (Fig. 275-1) Transthoracic echocardiography (TTE) is indicated to assess the mechanism of the MR and its hemodynamic severity. LV function can be assessed from LV end-diastolic and end-systolic volumes and EF. Observations can be made regarding leaflet structure and function, chordal integrity, LA and LV size, annular calcification, and regional and global LV systolic function. Doppler imaging should demonstrate the width or area of the color flow MR jet within the LA, the duration and intensity of the continuous wave Doppler signal, the pulmonary venous flow contour, the early peak mitral inflow velocity, and quantitative measures of regurgitant volume, RF, and effective regurgitant orifice area. In addition, the PA pressures (PAPs) can be estimated from the TR jet velocity. TTE is also indicated to follow the course of patients with chronic MR and to provide rapid assessment for any clinical change. Transesophageal echocardiography (TEE) provides greater anatomic detail than TTE (see Fig. 248-5). Exercise testing with TTE can be useful to assess exercise capacity as well as any dynamic change in MR severity, PA systolic pressures, and biventricular function, for patients in whom there is a discrepancy between clinical findings and the results of other noninvasive testing.

Chest X-Ray The LA and LV are the dominant chambers in chronic MR. Late in the course of the disease, the LA may be massively enlarged and forms the right border of the cardiac silhouette. Pulmonary venous congestion, interstitial edema, and Kerley B lines

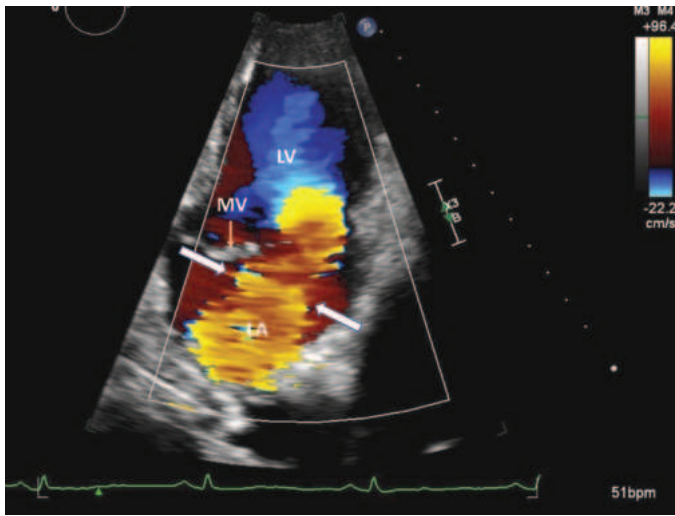


FIGURE 275-1 Mitral regurgitation. Apical two-chamber transthoracic color flow Doppler echocardiographic display of a broad systolic jet of severe mitral regurgitation (yellow stream between the two white arrows) from the left ventricle directed posteriorly into the left atrium. LA, left atrium; LV, left ventricle; MV, anterior leaflet of the mitral valve.

are sometimes noted. Marked calcification of the mitral leaflets occurs commonly in patients with long-standing, combined rheumatic MR and MS, as well as in patients with radiation-induced mitral valve disease. Calcification of the mitral annulus may be visualized, particularly

on the lateral view of the chest. Patients with acute severe MR may have asymmetric pulmonary edema if the regurgitant jet is directed predominantly to the orifice of an upper lobe pulmonary vein.

TREATMENT (FIGS. 275-2 AND 275-3)

Mitral Regurgitation

MEDICAL TREATMENT

The management of chronic severe MR depends to some degree on its cause. Anticoagulation with either warfarin or a direct oral agent (e.g., apixaban, rivaroxaban) should be provided if AF intervenes, as guided by the CHA₂DS₂-VASc risk score. The direct oral anticoagulants should not be used if moderate or severe rheumatic mitral stenosis is also present (**Ch. 274**); they are also not approved for use in patients with mechanical prosthetic heart valves. Cardioversion should be considered depending on the clinical context, AF chronicity, and LA size. In contrast to the acute setting, there are no large, long-term prospective studies to substantiate the use of vasodilators for the treatment of chronic, isolated severe primary MR with preserved LV systolic function *in the absence of systemic hypertension*. However, the severity of secondary MR in the setting of an ischemic or dilated cardiomyopathy may diminish with aggressive guideline-directed medical therapy (GDMT) of heart failure including the use of diuretics for decongestion, beta blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers, angiotensin-neprilysin inhibitors, mineralocorticoid receptor antagonists, sodium-glucose cotransporter

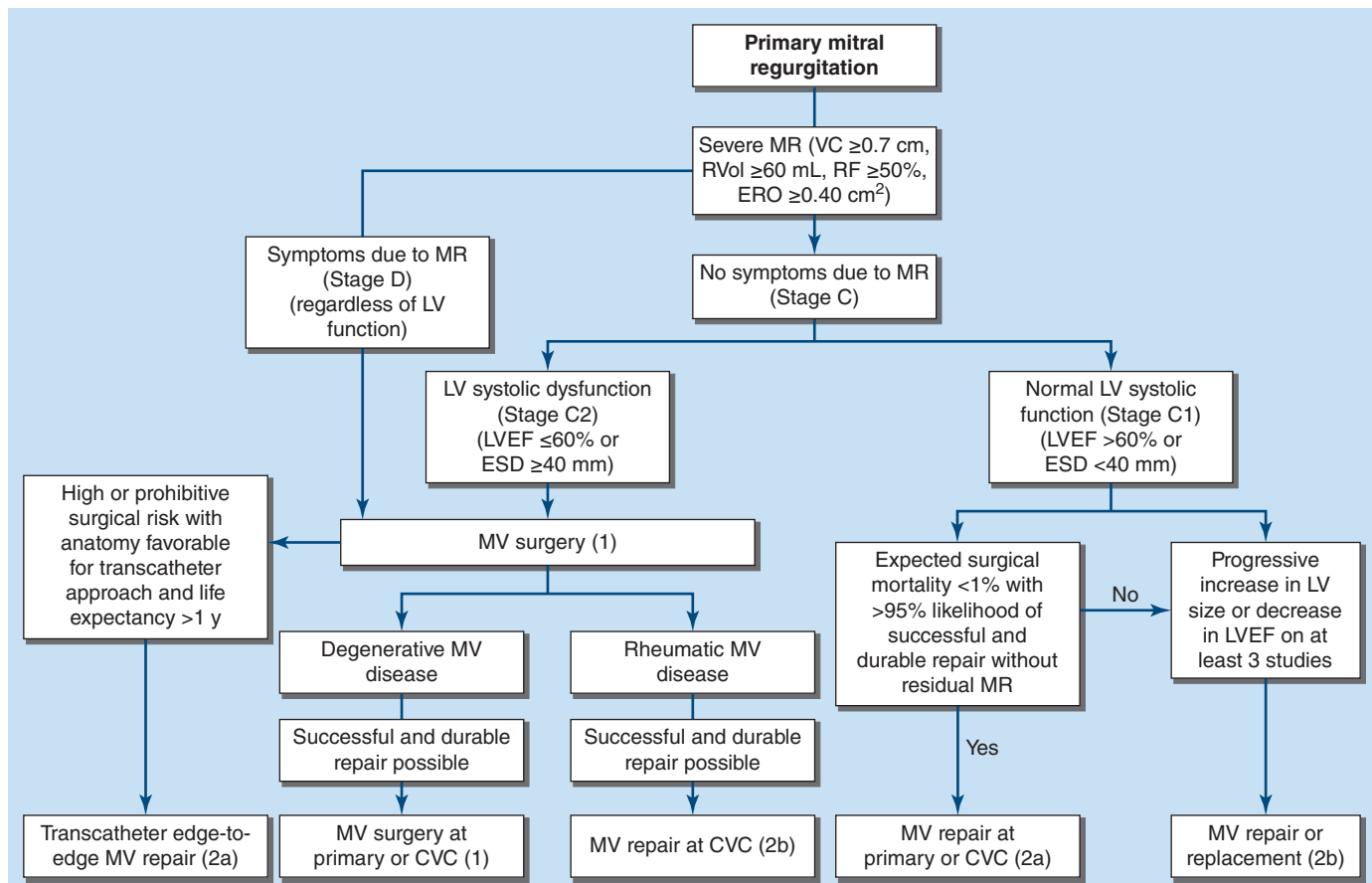


FIGURE 275-2 Management of primary mitral regurgitation (MR). See legend for **Fig. 272-4** for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Mitral valve repair is strongly preferred over valve replacement whenever feasible for surgical treatment of primary MR. Transcatheter edge-to-edge repair (TEER) is reserved for high or prohibitive surgical risk patients with appropriate anatomy on transesophageal imaging. CVC, comprehensive valve center; EF, ejection fraction; ERO, effective regurgitant orifice; ESD, end-systolic dimension; LV, left ventricular; MV, mitral valve; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta. (Reproduced with permission from CM Otto et al: ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021; 143(5):e72.)

2 inhibitors, and biventricular pacing (cardiac resynchronization therapy [CRT]) when indicated. Antibiotic prophylaxis for prevention of IE is indicated for MR patients with a prior history of IE. Asymptomatic patients with severe MR in sinus rhythm with normal LV size and systolic function should avoid isometric forms of exercise.

Patients with acute severe MR require urgent stabilization and preparation for surgery. Diuretics, intravenous vasodilators (particularly sodium nitroprusside), and even mechanical circulatory support may be needed for patients with post-MI papillary muscle rupture or other forms of acute severe MR.

SURGICAL TREATMENT

In the selection of patients with chronic, severe, primary MR for surgical treatment, the often slowly progressive nature of the condition must be balanced against the immediate and long-term risks associated with operation. These risks are significantly lower for primary valve repair than for valve replacement (Table 275-2). In a 2023 analysis of outcomes reported to the Society of Thoracic Surgeons Adult Cardiac Surgical Database, investigators reported a mean perioperative mortality risk of 1.16% (<0.5% for patients <65 years of age) for repair of primary MR. Repair usually consists of valve reconstruction using a variety of valvuloplasty techniques and insertion of an annuloplasty ring. Repair spares the patient the long-term adverse consequences of valve replacement, including thromboembolic and hemorrhagic complications in the case of mechanical prostheses and late valve failure necessitating repeat valve replacement in the case of bioprostheses. In addition,

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
MVR (isolated)	10,699	4.5
MVR + CAB	3509	9.6
MVRp	12,424	1.2
MVRp + CAB	4093	5.4

^aData are for calendar year 2018 during which 1088 participant groups reported a total of 287,872 procedures. Surgical mitral valve commissurotomy cases are included in the mitral valve repair procedures.

Abbreviations: CAB, coronary artery bypass; MVR, mitral valve replacement; MVRp, mitral valve repair.

Source: Adapted from ME Bowdish et al: Ann Thorac Surg 109:1646, 2020.

by preserving the integrity of the papillary muscles, subvalvular apparatus, and chordae tendineae, mitral repair and valvuloplasty maintain LV function to a relatively greater degree than does valve replacement.

Surgery for chronic severe primary MR is indicated once symptoms occur, especially if valve repair is feasible (Fig. 275-2). Surgery should also be recommended for asymptomatic patients with LV dysfunction characterized by an EF ≤60% or an LV end-systolic dimension (LV ESD) ≥40 mm. Other indications for early consideration of mitral valve repair in asymptomatic patients include a progressive decrease in LVEF or increase in LV ESD on serial imaging as well as mitral valve anatomy that would predict a >95% of a successful and durable repair in a low surgical risk patient.

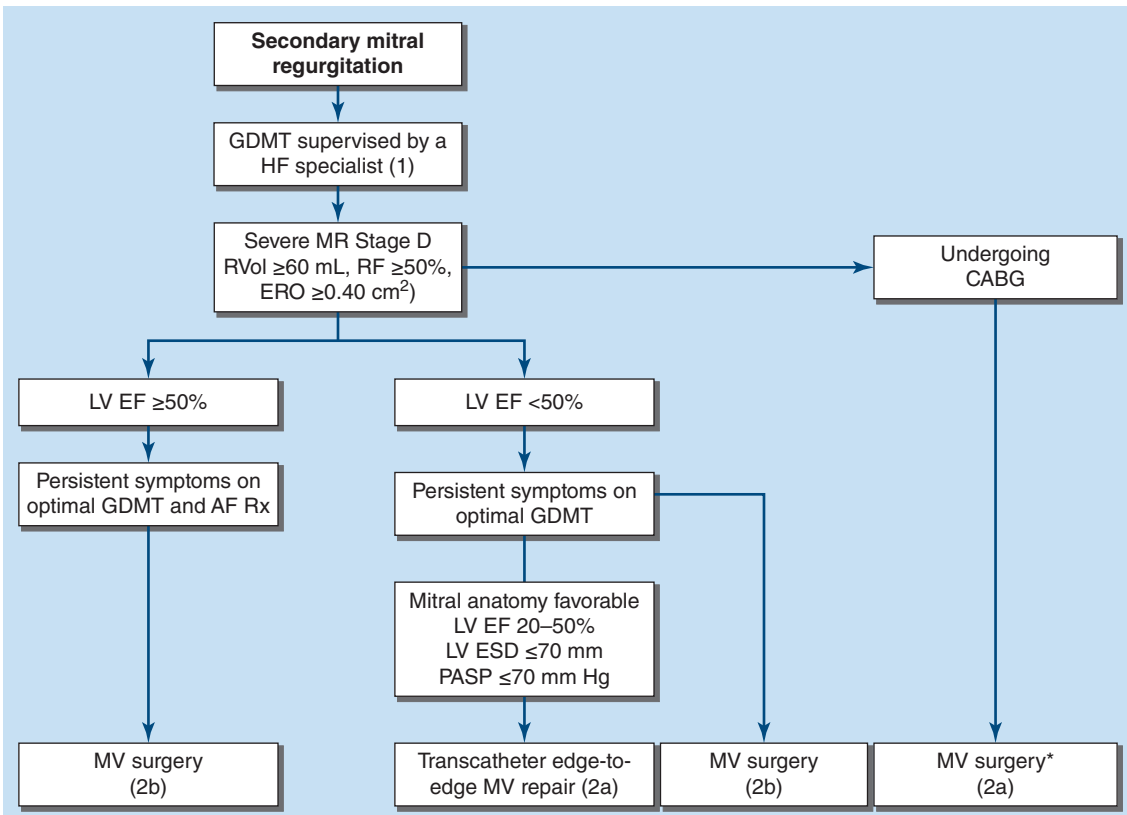


FIGURE 275-3 Management of secondary mitral regurgitation. See legend for Fig. 272-4 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Surgery is recommended for patients with left ventricular ejection fraction (LVEF) >50%. Transcatheter edge-to-edge repair (TEER) is reasonable in selected patients after guideline-directed management and therapy (GDMT) has been optimized. *MV replacement may be preferred over MV repair for ischemic MR; AF, atrial fibrillation; CABG, coronary artery bypass grafting; EF, ejection fraction; ERO, effective regurgitant orifice; ESD, end-systolic dimension; HF, heart failure; LV, left ventricular; MR, mitral regurgitation; MV, mitral valve; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; Rx, treatment. (Reproduced with permission from CM Otto et al: ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143(5):e72.)

These aggressive recommendations for surgery are predicated on the adverse long-term consequences of waiting for LV function to decline further as well as the outstanding results achievable with mitral valve repair by reference surgeons at high-volume centers. Indeed, the majority of patients <75 years of age with degenerative MR, normal LV systolic function, and no coronary artery disease (CAD) can now undergo successful and durable repair of degenerative MR (e.g., prolapse, flail) by an experienced surgeon at very low risk for perioperative death or major complication. Repair is feasible in up to 95% of patients with degenerative disease operated on by a high-volume surgeon in a referral center of excellence. Repair techniques include chordal transfer, creation of neochords, limited leaflet resection, and insertion of an annuloplasty band. Long-term durability is excellent; the incidence of reoperative surgery for failed primary repair is ~1% per year for the first 10 years after surgery. For patients with paroxysmal or persistent AF, left or biatrial maze surgery, or radiofrequency or cryoablative isolation of the pulmonary veins, along with left atrial appendage amputation, is performed to reduce the risk of recurrent postoperative AF and associated thrombus formation.

The surgical management of patients with secondary MR is more complicated. Surgery for patients with ischemic MR most often involves simultaneous coronary artery revascularization. Current surgical practice includes either annuloplasty repair with an undersized, rigid ring or chord-sparing valve replacement for patients with moderate or greater degrees of MR. Valve repair for ischemic MR is associated with lower perioperative mortality rates than valve replacement but significantly higher rates of recurrent MR over time. Thus, replacement may be preferred over repair in this context. In patients with ischemic MR and significantly impaired LV systolic function (EF <30%), the risk of surgery is higher, recovery of LV performance is incomplete, and long-term survival is reduced. Referral for surgery must be individualized and made only

after aggressive attempts to improve symptoms with GDMT and CRT, when indicated. The routine performance of surgical valve repair in patients with significant secondary MR due to a dilated cardiomyopathy has not been shown to improve long-term survival compared with optimal GDMT, especially in the era of quadruple medical therapy for heart failure with reduced EF. Patients with acute severe MR can often be stabilized temporarily with appropriate medical therapy, but surgical correction will be necessary emergently in the case of papillary muscle rupture and within days in most other settings.

When surgical treatment is contemplated, left and right heart catheterization and left ventriculography *may* be helpful in confirming the presence of severe MR in patients in whom there is a discrepancy between the clinical and TTE findings that cannot be resolved with TEE or CMR. Coronary angiography identifies patients who require concomitant coronary revascularization.

TRANSCATHETER MITRAL VALVE REPAIR AND REPLACEMENT

A transcatheter approach to the treatment of either primary or secondary MR may be feasible in selected patients with appropriate mitral valve anatomy. One approach involves the deployment of a clip delivered via transseptal puncture that grasps the leading edges of the mitral leaflets in their mid-portion (anterior scallop to posterior scallop). The length and width of the gap between the leading edges of the leaflets, as well as other considerations such as leaflet thickening and calcification, dictate patient eligibility. There are two commercially available transcatheter systems employing clip technology for the treatment of degenerative MR in symptomatic patients considered to be at high or prohibitive surgical risk (Fig. 275-4). Randomized trials of transcatheter

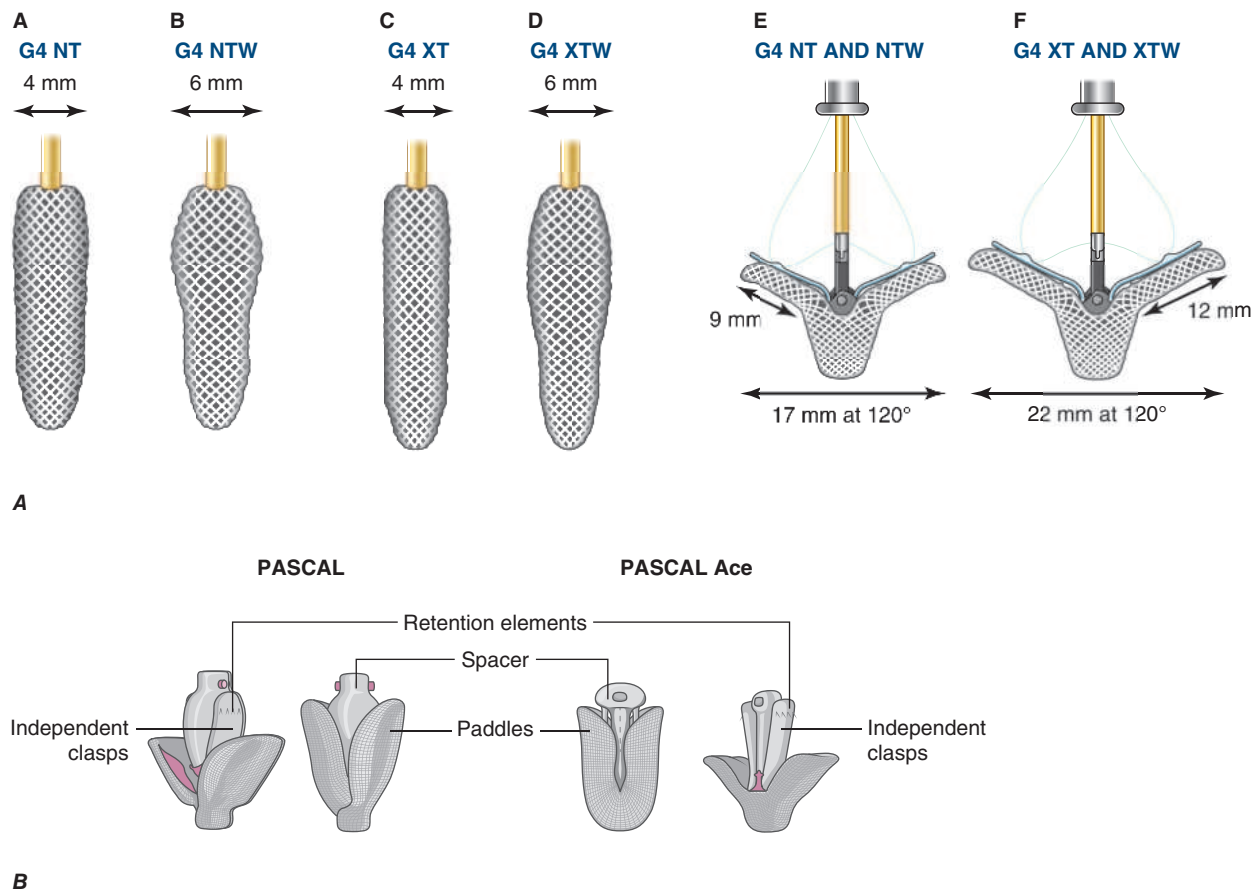


FIGURE 275-4 Clip devices used to grasp the free edges of the anterior and posterior leaflets in their midsections during transcatheter mitral valve repair of selected patients with mitral regurgitation. **A**, Fourth-generation of the first approved edge-to-edge repair device. **B**, System approved in 2022 includes a central spacer device and two paddles. The spacer is designed to reduce stress on the leaflets and preserve mitral valve area. (*MitraClip* is a trademark of Abbott or its related companies. *PASCAL* is an Edwards Lifesciences tradename.)

edge-to-edge repair (TEER) versus surgical repair are ongoing to determine if the extension of clip technology to low- and intermediate-risk surgical patients with significant degenerative MR is appropriate. The TEER system is also approved for the treatment of heart failure patients with secondary MR. The results of transthoracic and transesophageal echocardiographic imaging are critical to patient selection, along with an assessment of the adequacy of GDMT for heart failure. The use of TEER with a clip device in addition to medical therapy was shown to be superior to medical therapy alone in a trial involving symptomatic heart failure patients with reduced EF and at least moderately severe secondary MR followed through 5 years. Patients treated with the clip device had significantly lower rates of heart failure hospitalizations and all-cause mortality than those treated medically. This was the first randomized trial to show a survival benefit in patients with heart failure and secondary MR. There has been a rapid expansion over the past 5 years in both the number of sites offering mitral valve TEER and the number of cases reported to the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry.

Other transcatheter approaches to mitral valve repair have included the deployment of a device within the coronary sinus that can be adjusted to reduce mitral annular circumference and the effective orifice area of the valve much like a surgically implanted ring. Variations in the anatomic relationship of the coronary sinus to the mitral annulus and circumflex coronary artery have limited the applicability of this technique. Attempts to reduce the septal-lateral dimension of a dilated annulus using adjustable cords placed across the LV in a subvalvular location have been investigated. Construction of neochords to the mitral leaflets under TEE guidance using a system delivered via the cardiac apex has also been studied. Investigational experience with transcatheter mitral valve replacement systems remains in early clinical stages, although the field is evolving rapidly. Many high surgical risk patients are not candidates for transcatheter mitral valve repair, and thus, there is keen interest in refining this technology. Challenges with transseptal delivery and LV outflow tract obstruction from the devices used have prompted iterative changes in the systems utilized in early feasibility studies.

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276

Mitral Valve Prolapse

Patrick T. O’Gara, Joseph Loscalzo

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in **Chaps. 44 and 246**; of electrocardiography (ECG) in **Chap. 247**; of echocardiography and other noninvasive imaging techniques in **Chap. 241**; and of cardiac catheterization and angiography in **Chap. 249**.

MITRAL VALVE PROLAPSE

Mitral valve prolapse (MVP), also variously termed the *systolic click-murmur syndrome*, *Barlow’s syndrome* (**Fig. 276-1**), *floppy-valve syndrome*, and *billowing mitral leaflet syndrome*, is a relatively common but highly variable clinical syndrome resulting from diverse pathologic mechanisms affecting the mitral valve apparatus. Among these are excessive or redundant mitral leaflet tissue, which is commonly associated with myxomatous degeneration and greatly increased concentrations of certain glycosaminoglycans. MVP is the most common abnormality leading to primary mitral regurgitation (MR) and mitral valve repair surgery (**see Chap. 275**).

In most patients with MVP, the cause is unknown, but in some, it appears to be genetically determined. A reduction in the production of type III collagen has been implicated, and electron microscopy has revealed fragmentation of collagen fibrils. A meta-analysis of six

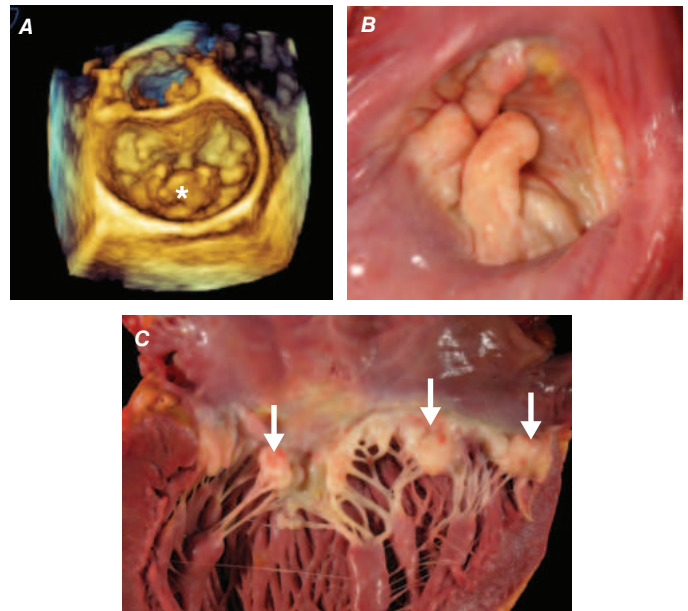


FIGURE 276-1 Mitral valve prolapse. Myxomatous thickening and prolapse of the mitral valve can occur in isolation in 2–3% of the general population or may be associated with heritable connective tissue disorders, such as Marfan syndrome. Myxomatous degeneration of the valve predisposes to severe regurgitation and chordal rupture and is a frequent indication for mitral valve repair or replacement. Prolapse can affect one or both leaflets, to varying degrees. **A.** Three-dimensional transesophageal echocardiogram showing a myxomatous mitral valve from the left atrial *en face* aspect. There is billowing and prolapse of the entire middle scallop of the posterior leaflet (asterisk). (Figure courtesy of Douglas C. Shook, MD, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women’s Hospital.) **B.** The posterior leaflet of the mitral valve demonstrates marked prolapse and hoarding in all segments and severe redundancy in this postmortem photograph taken from the vantage point of the left atrium. **C.** Opening the left heart reveals prominent mitral leaflet hoarding (arrows). The chordae are focally thickened but are not fused as would be the case in rheumatic valve disease. (Used with permission from JC Wu, RF Padera: *Clinicopathologic correlates*, in *Atlas of Echocardiography*, 2nd ed, SD Solomon [ed], E Braunwald [series ed]. Philadelphia, Current Medicine Group LLC, 2008. p 363.)

genome-wide association studies and 4884 MVP cases identified 14 genetic loci associated with MVP. Candidate genes included *LMCD1*, *SPTBN1*, *LTBP2*, *TGFB2*, *NMB*, and *ALPK3*. A polygenic risk score improved the performance of a clinical risk prediction model for the development of MVP, although overall performance was modest. Other work has identified genetic associations with *LMNA*, *FLNC*, and *FLNA*, which are often expressed as cardiomyopathies.

MVP is a frequent finding in patients with heritable disorders of connective tissue, including Marfan syndrome (**Chap. 425**), osteogenesis imperfecta, and Ehlers-Danlos syndrome. MVP may be associated with thoracic skeletal deformities similar to but not as severe as those in Marfan syndrome, such as a high-arched palate and alterations of the chest and thoracic spine, including kyphosis and the so-called straight back syndrome. Other associated features can include a history of inguinal hernias, joint dislocations, meniscal tears, and easy bruisability.

In most patients with MVP, myxomatous degeneration is confined to the mitral valve, although the tricuspid and aortic valves may also be affected. Prolapse can affect one or both leaflets. The posterior mitral leaflet is usually more affected than the anterior, and the mitral valve annulus is often dilated. In many patients, elongated, redundant, or ruptured chordae tendineae cause or contribute to the regurgitation.

MVP also may occur rarely as a sequel to acute rheumatic fever, in ischemic heart disease, and in various cardiomyopathies (see above), as well as in 20% of patients with ostium secundum atrial septal defect.

MVP may lead to excessive stress on the papillary muscles, leading to localized ischemia, infarction, and replacement fibrosis. The latter, which may be a nidus for ventricular arrhythmias, may be visible on cardiac magnetic resonance imaging as late gadolinium enhancement and occurs in the absence of coronary artery disease. Rupture of chordae tendineae and progressive annular dilation and calcification contribute to valvular regurgitation, which then places more stress on the diseased mitral valve apparatus, thereby creating a vicious cycle.

■ CLINICAL FEATURES

MVP is more common in women than men and occurs most frequently between the ages of 15 and 30 years; the clinical course is most often benign. MVP may also be observed in older (>50 years) patients, often men, in whom MR is often more severe because of chordal rupture and requires surgical treatment. There is an increased familial incidence for some patients, suggesting an autosomal dominant form of inheritance with incomplete penetrance. MVP varies in its clinical expression, ranging from only a systolic click and murmur with mild prolapse of the posterior leaflet to severe MR due to chordal rupture and leaflet flail. The degree of myxomatous change of the leaflets can also vary widely. In many patients, the condition progresses over years or decades; in others, it worsens rapidly as a result of chordal rupture or endocarditis.

Most patients are asymptomatic and remain so for their entire lives. However, in North America, MVP is now the most common cause of isolated severe MR requiring surgical treatment. Arrhythmias, most commonly ventricular premature contractions and paroxysmal supraventricular and ventricular tachycardia, as well as atrial fibrillation (AF), have been reported and may cause palpitations, light-headedness, and syncope. Sudden death is a very rare complication and occurs most often in patients with severe MR and depressed left ventricle (LV) systolic function, although it can occur in individuals with normal LV size and function. A small subset of MVP patients with high-grade ventricular ectopy has been identified with phenotypic features including electrocardiographic inferior-apical T-wave abnormalities, high-density premature ventricular complexes at rest, mitral annular disjunction (defined as abnormal atrial displacement of the mitral valve leaflet hinge point), and papillary muscle fibrosis on cardiac magnetic resonance imaging (see above). In addition, there may be an excess risk of sudden death among patients with a flail leaflet. Most of these patients have severe MR. Many patients with MVP have chest pain that can be difficult to evaluate; it is often substernal, prolonged, and not related to exertion,

but may rarely resemble angina pectoris. Transient cerebral ischemic attacks secondary to emboli from the mitral valve due to endothelial disruption have been reported. Infective endocarditis may occur in patients with MR and/or leaflet thickening.

Auscultation A frequent finding is the mid- or late (nonejection) systolic click, which occurs 0.14 s or more after S_1 and is thought to be generated by the sudden tensing of slack, elongated chordae tendineae or by the prolapsing mitral leaflet when it reaches its maximal excursion. Systolic clicks may be multiple and may be followed by a high-pitched, mid-late systolic crescendo-decrescendo murmur, which occasionally is “whooping” or “honking” and is heard best at the apex. Radiation of the murmur will depend on the involved leaflet. With posterior leaflet prolapse, the jet of MR is directed anteriorly and the murmur will radiate to the base of the heart. With anterior leaflet involvement, the jet of MR is directed posteriorly and the murmur will radiate to the axilla and back. The click and murmur occur earlier with standing, during the strain phase of the Valsalva maneuver and with any intervention that decreases LV volume (preload), exaggerating the propensity of the leaflet to prolapse. Conversely, squatting and isometric exercises, which increase LV volume, diminish MVP; the click-murmur complex is delayed, moves away from S_1 , and may even disappear. Some patients have a mid-systolic click without a murmur; others have a murmur without a click. Still others have both sounds at different times.

LABORATORY EXAMINATION

The ECG most commonly is normal but may show biphasic or inverted T waves in leads II, III, and aVF and, occasionally, supra-ventricular or ventricular premature beats. Transthoracic echocardiography (TTE) is particularly effective in identifying the abnormal position and prolapse of the mitral valve leaflets. A useful echocardiographic definition of MVP is systolic displacement (in the parasternal long axis view) of the belly of the mitral valve leaflets by at least 2 mm into the left atrium (LA) superior to the plane of the mitral annulus. There can be prolapse of one or both leaflets (**Fig. 276-2**). Color flow and continuous wave Doppler imaging is helpful to evaluate the associated MR and provide estimates of severity. The jet lesion of MR due to MVP is most often eccentric, and assessment of the effective regurgitant orifice area and regurgitant volume can be difficult with standard techniques. Both three-dimensional echocardiography and cardiac magnetic resonance imaging can provide more precise determinations of LV volumes. Transesophageal echocardiography (TEE) is indicated when more accurate anatomic information is required and is performed routinely for intraoperative guidance during surgical or transcatheter valve repair. Exercise testing can be performed when there is uncertainty regarding functional capacity. It is often combined with rest and immediate poststress TTE to assess LV and right ventricular (RV) function and the dynamic nature of MR and pulmonary artery pressures. Left ventriculography done at the time

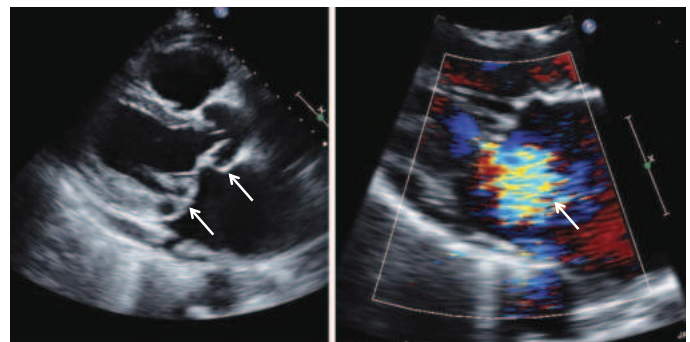


FIGURE 276-2 Barlow's valve with classic mitral valve prolapse, as seen on transthoracic echocardiogram in parasternal long-axis windows. Left: parasternal long-axis window, showing both myxomatous leaflets (arrows) billowing into the left atrium in late systole. Right: same window with color Doppler showing significant mitral regurgitation (arrow) in systole. (Courtesy of Justina Wu, MD, PhD.)

of right and left heart catheterization is rarely necessary but can also show prolapse of the posterior and sometimes of both mitral valve leaflets.

TREATMENT

Mitral Valve Prolapse

Infective endocarditis prophylaxis is indicated for patients with a prior history of endocarditis. Beta blockers sometimes relieve chest pain and control palpitations. Decisions regarding anticoagulation for stroke prevention in AF should be based on the CHA₂DS₂-VASC score and an assessment of bleeding risk. If the patient is symptomatic from severe MR, mitral valve repair is indicated (see Fig. 275-2). Other indications for surgery for MVP with severe primary MR include findings of established or progressive LV systolic dysfunction. Surgery can also be considered for low-risk asymptomatic patients in whom a successful and durable repair can be achieved with at least 95% likelihood by an expert surgeon. Mitral valve repair is preferred over replacement in patients with MVP or flail mitral leaflet (see Table 275-2); technical success is dependent not only on the anatomic findings but also on the skill and experience of the surgeon. Repair of isolated posterior leaflet prolapse is usually straightforward, but increasingly more complex pathologies (e.g., anterior leaflet prolapse, bileaflet prolapse, Barlow's deformity) require advanced skills. Careful pre- and intraoperative TEE imaging is an important component of patient evaluation and surgical planning. Transcatheter edge-to-edge repair (TEER) using one of two commercially available systems to grasp the anterior and posterior leaflets together can be considered for treatment of symptomatic patients at prohibitive or high surgical risk with severe primary MR due to MVP (see Chap. 275 and Fig. 275-4). Most often, the MR will be reduced in severity but not eliminated. Nevertheless, symptom status and indices of LV size and function can be improved with this approach, which is now offered at >540 specialized sites in the United States. Reported hospital mortality rates following the procedure are <2%. Transcatheter replacement devices remain under active investigation but are not yet approved for use in the United States (see Chap. 275).

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TABLE 277-1 Causes of Tricuspid Valve Diseases

VALVE LESION	ETIOLOGIES
Tricuspid stenosis	Rheumatic Congenital
Tricuspid regurgitation	Primary (organic, leaflet, or chordal related) Rheumatic Endocarditis Myxomatous (TVP) Carcinoid Radiation Congenital (Ebstein's) Trauma (including that due to RV endomyocardial biopsy) Secondary (functional, atrial, and/or ventricular) RV and/or tricuspid annular dilation due to multiple causes (e.g., long-standing pulmonary HTN, remodeling post-RV MI, left-sided heart disease, cardiomyopathy, AF [atrial functional tricuspid regurgitation]) CIED related Leaflet impingement, adherence, laceration, perforation, avulsion; chordal entrapment

Abbreviations: AF, atrial fibrillation; CIED, cardiac implanted electronic device; HTN, hypertension; MI, myocardial infarction; RV, right ventricular; TVP, tricuspid valve prolapse.

Hemodynamically significant TS occurs in 5–10% of patients with severe MS; rheumatic TS is commonly associated with some degree of tricuspid regurgitation (TR). Nonrheumatic causes of TS are rare.

PATHOPHYSIOLOGY

A diastolic pressure gradient between the right atrium (RA) and right ventricle (RV) defines TS. It is augmented when the transvalvular blood flow increases during inspiration and declines during expiration. A mean diastolic pressure gradient of 4 mmHg is usually sufficient to elevate the mean RA pressure to levels that result in systemic venous congestion. Unless sodium intake has been restricted and diuretics administered, this venous congestion is associated with hepatomegaly, ascites, and edema, sometimes severe. In patients with sinus rhythm, the RA *a* wave may be extremely tall and may even approach the level of the RV systolic pressure. The *y* descent is prolonged. The cardiac output (CO) at rest is usually depressed, and it fails to rise during exercise. The low CO is responsible for the normal or only slightly elevated left atrial (LA), pulmonary artery (PA), and RV systolic pressures despite the presence of MS. Thus, the presence of TS can mask the hemodynamic and clinical features of any associated MS.

SYMPTOMS

Because the development of MS generally precedes that of TS, many patients initially have symptoms of pulmonary congestion and fatigue. Characteristically, patients with severe TS complain of relatively little dyspnea for the degree of hepatomegaly, ascites, and edema that they have. However, fatigue secondary to a low CO and discomfort due to signs of right-sided congestion such as hepatomegaly and ascites are common in patients with advanced TS and/or TR. In some patients, TS may be suspected for the first time when symptoms of right-sided failure persist after an adequate mitral commissurotomy.

PHYSICAL FINDINGS

Because TS usually occurs in the presence of other obvious valvular disease, the diagnosis may be missed unless it is considered. Severe TS is associated with marked hepatic congestion, often resulting in cirrhosis, jaundice, serious malnutrition, anasarca, and ascites. Congestive hepatomegaly and, in cases of severe tricuspid valve disease, splenomegaly are present. The jugular veins are distended, and in patients with sinus rhythm, there may be giant *a* waves. The *v* waves are less conspicuous, and because tricuspid obstruction impedes RA emptying during diastole, there is a slow *y* descent. In patients with sinus rhythm, there may be prominent presystolic pulsations of the enlarged liver as well.

277

Tricuspid Valve Disease

Patrick T. O'Gara, Joseph Loscalzo

TRICUSPID STENOSIS

Tricuspid stenosis (TS), which is much less prevalent than mitral stenosis (MS) in North America and Western Europe, is generally rheumatic in origin and is more common in women than men (Table 277-1). It does not occur as an isolated lesion and is usually associated with MS.

On auscultation, an opening snap (OS) of the tricuspid valve may rarely be heard ~0.06 s after pulmonic valve closure. The diastolic murmur of TS has many of the qualities of the diastolic murmur of MS, and because TS almost always occurs in the presence of MS, it may be missed. However, the tricuspid murmur is generally heard best along the left lower sternal border and over the xiphoid process and is most prominent during presystole in patients with sinus rhythm. The murmur of TS is augmented during inspiration, and it is reduced during expiration and particularly during the strain phase of the Valsalva maneuver, when tricuspid transvalvular flow is reduced.

LABORATORY EXAMINATION

The electrocardiogram (ECG) features of RA enlargement (see Fig. 247-8) include tall, peaked P waves in lead II, as well as prominent, upright P waves in lead V₁. The *absence* of ECG evidence of RV hypertrophy (RVH) in a patient with right-sided heart failure who is believed to have MS should suggest associated tricuspid valve disease. The chest x-ray in patients with combined TS and MS shows particular prominence of the RA and superior vena cava without much enlargement of the PA and with less evidence of pulmonary vascular congestion than occurs in patients with isolated MS; engorgement of the azygos vein can often be appreciated. On transthoracic echocardiographic (TTE) examination, the tricuspid valve is usually thickened and domes in diastole; the transvalvular gradient can be estimated by continuous wave Doppler echocardiography. Severe TS is characterized by a valve area ≤ 1 cm² or pressure half-time of ≥ 190 ms. The RA and inferior vena cava (IVC) are enlarged. TTE provides additional information regarding the severity of any associated TR, mitral valve structure and function, left ventricular (LV) and RV size and function, and PA pressure. Cardiac catheterization is not routinely necessary for assessment of TS.

TREATMENT

Tricuspid Stenosis

Patients with TS generally exhibit marked systemic venous congestion; salt restriction, bed rest, and diuretic therapy are required during the preoperative period. Such a preparatory period may

diminish hepatic congestion and thereby improve hepatic function sufficiently so that the risks of operation, particularly bleeding, are diminished. Surgical relief of the TS should be carried out, preferably at the time of surgical mitral commissurotomy or mitral valve replacement (MVR) for mitral valve disease, in patients with moderate or severe TS who have mean diastolic pressure gradients exceeding ~4 mmHg and tricuspid orifice areas <1.5 – 2 cm². TS is almost always accompanied by significant TR. Operative repair may permit substantial improvement of tricuspid valve function. If repair cannot be accomplished, the tricuspid valve may have to be replaced. Meta-analysis has shown no difference in overall survival between mechanical and tissue valve replacement. Mechanical valves in the tricuspid position are more prone to thromboembolic complications than in other positions. Percutaneous tricuspid balloon commissurotomy for isolated severe TS without significant TR is very rarely performed.

TRICUSPID REGURGITATION

More than 85% of TR cases encountered in clinical practice are secondary (functional) in nature and related to tricuspid annular dilation and leaflet tethering in the setting of RV remodeling caused by pressure or volume overload (or both), myocardial infarction (MI), or trauma (Table 277-1). Secondary TR is commonly seen in the late stages of heart failure due to rheumatic or congenital heart disease with severe PA hypertension (PA systolic pressure >55 mmHg), as well as in other types of left-sided valvular (e.g., mitral regurgitation) or myocardial diseases (e.g., ischemic and idiopathic dilated cardiomyopathies). TR can often emerge in the setting of new-onset atrial fibrillation (AF), particularly in older patients (atrial functional TR). Rheumatic fever may produce primary TR, often associated with TS. Tricuspid valve prolapse, carcinoid heart disease, endomyocardial fibrosis, radiation, infective endocarditis, and leaflet trauma can also produce primary TR. Less commonly, primary TR results from congenitally deformed tricuspid valves and can occur with defects of the atrioventricular canal, as well as with Ebstein's malformation of the tricuspid valve (Chap. 280). A third category of TR is that associated with cardiac implantable electronic device (CIED) leads from pacemakers or defibrillators. When placed across the tricuspid valve, the leads can result

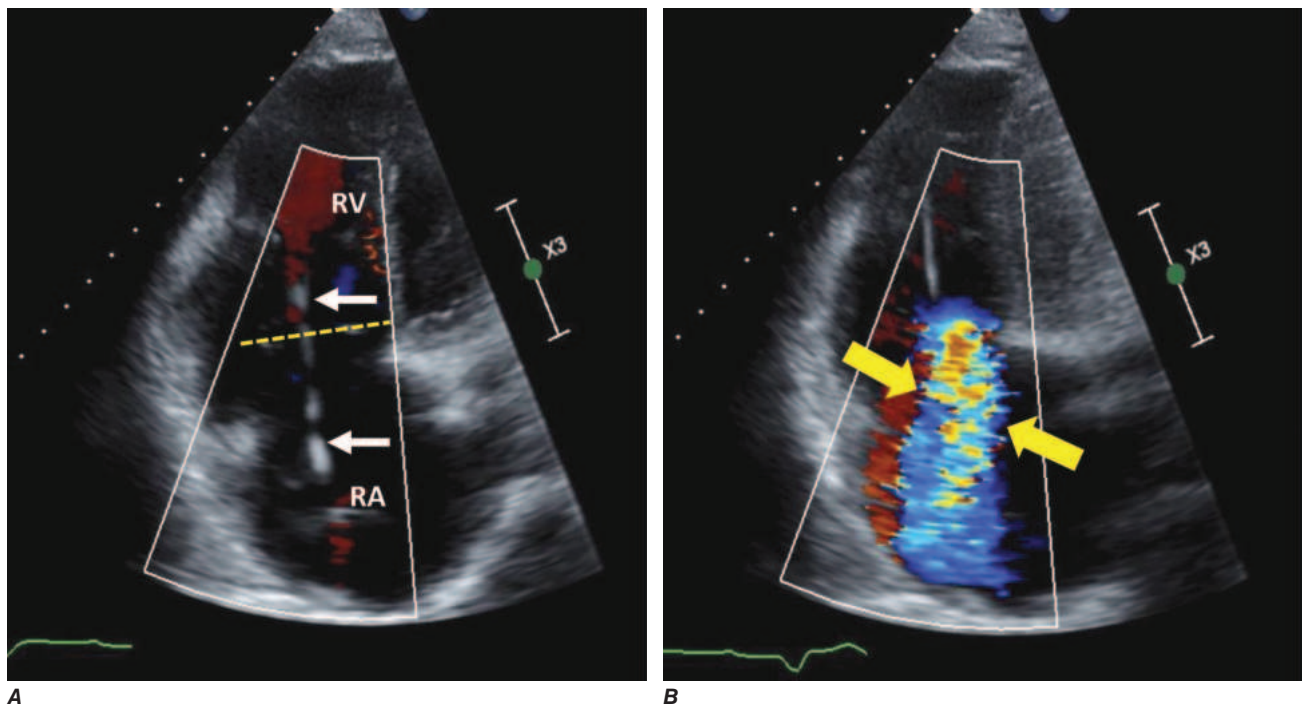


FIGURE 277-1 Tricuspid regurgitation. **A.** Transthoracic apical two-chamber view showing right atrium on bottom and right ventricle on top. There is a pacemaker lead (white arrows) traversing the tricuspid valve. The plane of tricuspid valve closure is shown by the dotted yellow line. **B.** Corresponding color flow Doppler image in systole shows a broad jet of severe tricuspid regurgitation (between the yellow arrows) refluxing into the right atrium. RA, right atrium; RV right ventricle.

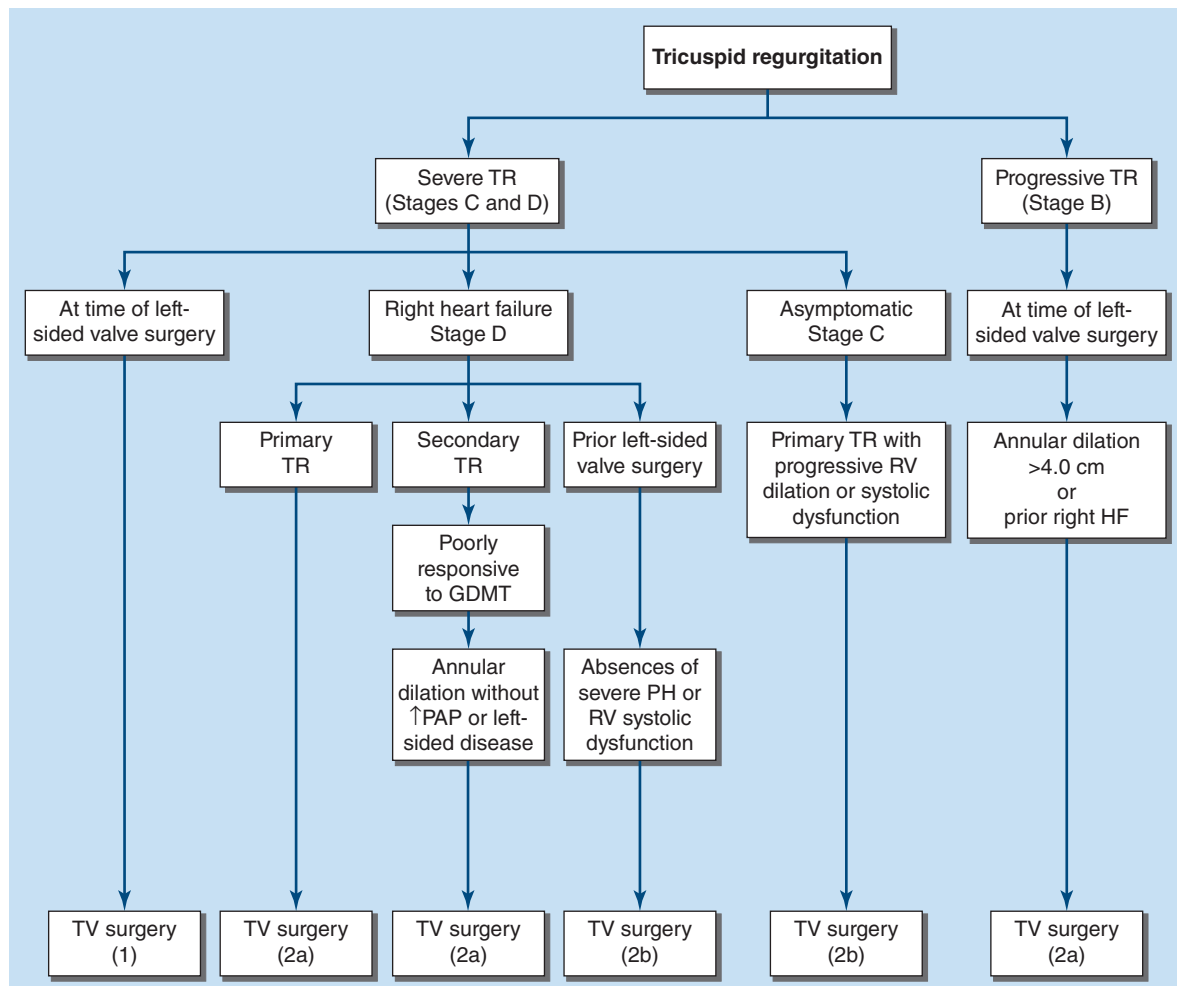


FIGURE 277-2 Management of tricuspid regurgitation. See legend for Fig. 272-4 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. GDMT, guideline-directed management and therapy; HF, heart failure; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RV, right ventricular; TR, tricuspid regurgitation; TV, tricuspid valve. Annular dilation is defined by >40 mm on transthoracic echocardiography (>21 mm/m²) or >70 mm on direct intraoperative measurement. (Reproduced with permission from CM Otto et al: 2020 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 143:e72, 2021.)

in leaflet entrapment or perforation. In addition, pacing from the right ventricular apex can result in dyssynchronous ventricular contraction and functional TR.

■ PATHOPHYSIOLOGY

The incompetent tricuspid valve allows blood to flow backward from the RV into the RA, the volume of which is dependent on the driving pressure (i.e., RV systolic pressure) and the size of the regurgitant orifice. The severity and physical signs of TR can vary as a function of PA systolic pressure (in the absence of RV outflow tract stenosis), the dimensions of the tricuspid valve annulus, the respiratory cycle-dependent changes in RV preload, and RA compliance. RV filling is increased during inspiration. With TR, forward CO is reduced and does not augment with exercise. Significant degrees of TR will lead to RA enlargement and elevation of the RA and jugular venous pressures with prominent *c-v* waves in the pulse tracings. Progressively severe TR can lead to “ventricularization” of the RA wave form (see Fig. 246-1B). Severe TR is also characterized by RV dilation (RV volume overload) and eventual systolic dysfunction, the progression of which can be accelerated by a concomitant pressure load from PA hypertension or by myocardial fibrosis from previous injury.

■ SYMPTOMS

Mild or moderate degrees of TR are usually well tolerated in the absence of other hemodynamic disturbances. Because TR often coexists with left-sided valve lesions, LV dysfunction, and/or PA

hypertension, symptoms related to these lesions may dominate the clinical picture. Atrial functional TR due to atrial fibrillation is usually accompanied by palpitations. Fatigue and exertional dyspnea owing to reduced forward CO are early symptoms of isolated, severe TR. As the disease progresses and RV function declines, patients may report cervical pulsations, abdominal fullness/bloating, diminished appetite, and muscle wasting, although with progressive weight gain and painful swelling of the lower extremities.

■ PHYSICAL FINDINGS

The neck veins in patients with severe TR are distended with prominent *c-v* waves and rapid *y* descents (in the absence of TS). TR is more often diagnosed by examination of the neck veins than by auscultation of the heart sounds. Other findings may include marked hepatomegaly with systolic pulsations, ascites, pleural effusions, edema, and a positive hepatojugular reflux sign. A prominent RV pulsation in the left parasternal region and a blowing holosystolic murmur along the lower left sternal margin, which may be intensified during inspiration (Carvallo’s sign) and reduced during expiration or the strain phase of the Valsalva maneuver, are characteristic findings. The murmur of TR may sometimes be confused with that of mitral regurgitation (MR) unless attention is paid to its variation during the respiratory cycle and the extent of RV enlargement is appreciated. AF may be the driver of TR or may emerge later in the disease with ventricular and atrial remodeling.

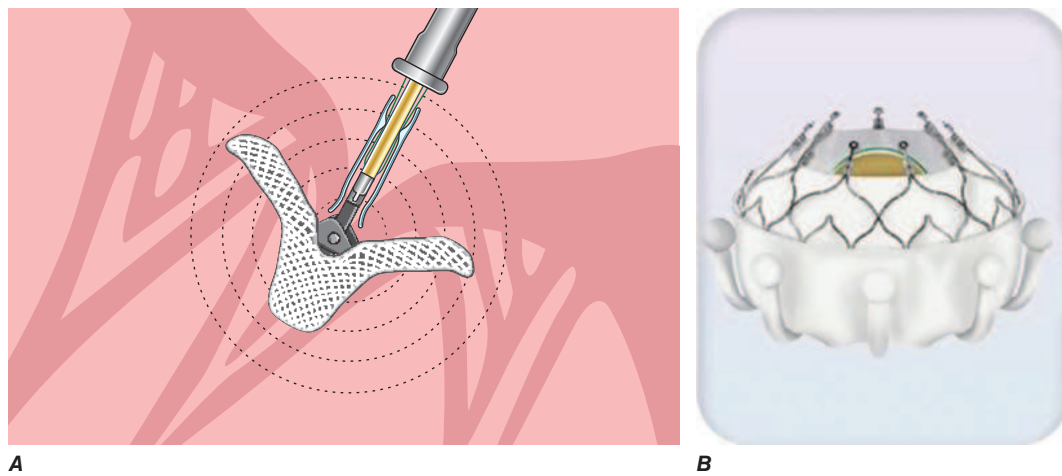


FIGURE 277-3 Transcatheter tricuspid valve (TV) repair and replacement. **A.** Shown is a clip device that can be used to grasp the leading edges of the TV leaflets to reduce the severity of tricuspid regurgitation (TR) by decreasing the effective orifice area of the valve. (*TriClip* is a trademark of Abbott or its related companies.) **B.** Bioprosthesis heart valve replacement approved for percutaneous treatment of severe TR is selected for high or prohibitive surgical risk patients. (*EVOQUE* is a trademark of Edwards Lifesciences.)

LABORATORY EXAMINATION

The ECG may show changes characteristic of the lesion responsible for the TR, e.g., an inferior Q-wave MI suggestive of a prior RV MI, RVH, or a bizarre right bundle branch block-type pattern with preexcitation in patients with Ebstein's anomaly. ECG signs of RA enlargement may be present in patients with sinus rhythm; AF is frequently noted. The chest x-ray may show RA and RV enlargement, depending on the chronicity and severity of TR. TTE is usually definitive with demonstration of RA dilation and RV volume overload and prolapsing, flail, scarred, or displaced/tethered tricuspid leaflets with annular dilatation; the diagnosis and assessment of TR can be made by color flow Doppler imaging (see Figs. 248-8 and 277-1). Severe TR is accompanied by hepatic vein systolic flow reversal. Continuous wave Doppler of the TR velocity profile is useful in estimating PA systolic pressure, except when the TR is very severe and the jet velocity is blunted by rapidly increasing RA pressure. Accurate assessment of TR severity, PA pressures, and RV size and systolic function with TTE can be quite challenging in many patients. Real-time three-dimensional echocardiography and cardiac magnetic resonance (CMR) imaging provide alternative imaging modalities to aid in the assessment of TR severity, although they are not widely available. In patients with severe TR, the CO is usually markedly reduced, and the RA pressure pulse may not exhibit an *x* descent during early systole but rather show a prominent *c-v* wave with a rapid *y* descent. The mean RA and RV end-diastolic pressures are often elevated. Exercise testing can be used to assess functional capacity in patients with asymptomatic severe TR. The prognostic significance of exercise-induced changes in TR severity and RV function has not been well studied. (See Fig. 277-1.)

TREATMENT

Tricuspid Regurgitation (Fig. 277-2)

Diuretics can be useful for patients with severe TR and signs of right heart failure. An aldosterone antagonist may be particularly helpful because many patients have secondary hyperaldosteronism from marked hepatic congestion. Therapies to reduce elevated PA pressures and/or pulmonary vascular resistance, including those targeted at left-sided heart disease, can also be considered for patients with PA hypertension and severe secondary TR. Tricuspid valve surgery is recommended for patients with *severe TR* who are undergoing left-sided valve surgery and is also undertaken frequently for treatment of even moderate TR in patients undergoing left-sided valve surgery especially those with tricuspid annular dilation (>40 mm), a history of right heart failure, or PA hypertension.

Operation most often comprises repair rather than replacement in these settings and has become more routine in many surgical centers. In a randomized trial of tricuspid valve annuloplasty surgery at the time of mitral valve surgery for degenerative MR in patients with *moderate TR* or *mild TR with annular dilation*, there was a significant reduction in the 2-year incidence of a composite endpoint of reoperation, progression of TR, or all-cause death among those who underwent tricuspid surgery versus those who had mitral valve surgery alone. The composite endpoint was driven by a reduction in the progression of TR. Surgery may also infrequently be required for treatment of severe, primary TR with right heart failure not responsive to standard medical therapy or because of progressively declining RV systolic function. Reported perioperative mortality rates for isolated tricuspid valve surgery (repair and replacement) are high (~8–9%) and likely are influenced by the hazards encountered during reoperation on patients who have undergone previous left-sided valve surgery and have reduced RV function.

There have been several recent advances in the application of transcatheter tricuspid valve repair and replacement techniques in patients with severe TR and high or prohibitive surgical risk. In a randomized trial of percutaneous transcatheter edge-to-edge repair versus medical therapy, clip repair resulted in a significant reduction in TR severity and improvement in quality-of-life scores, but no differences in all-cause mortality or hospitalization for heart failure over 1-year follow-up. The U.S. Food and Drug Administration approved the use of a transcatheter tricuspid valve replacement system in early 2024 based on favorable hemodynamic, echocardiographic, clinical, and quality-of-life results from prospective single-arm studies. (See Figure 277-3.)

FURTHER READING

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- KODALI S et al: Transfemoral tricuspid valve replacement and one-year outcomes: The TRISCEND study. *Eur Heart J* 44:4862, 2023.
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- SORAJJA P et al: Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med* 388:1833, 2023.

278

Pulmonic Valve Disease

Patrick T. O’Gara, Joseph Loscalzo

PULMONIC STENOSIS

Pulmonic valve stenosis (PS) is essentially a congenital disorder (Table 278-1). With isolated PS, the valve is typically domed. Dysplastic pulmonic valves are seen as part of the Noonan syndrome (Chap. 292), which maps to chromosome 12. Mutations in the *PTPN1* gene are associated with about half of all cases of Noonan syndrome. Much less common etiologies include carcinoid and obstructing tumors or bulky vegetations. The pulmonic valve is only very rarely affected by the rheumatic process.

■ PATHOPHYSIOLOGY

PS is defined hemodynamically by a systolic pressure gradient between the right ventricle (RV) and the main pulmonary artery (PA). RV hypertrophy (RVH) develops as a consequence of sustained obstruction to RV outflow, and systolic ejection is prolonged. Compared with the ability of the LV to compensate for the pressure overload imposed by aortic stenosis (AS), RV dysfunction from afterload mismatch occurs earlier in the course of PS and at lower peak systolic pressures, because the RV adapts less well to this type of hemodynamic burden. With normal systolic function and cardiac output (CO), severe PS is defined by a peak systolic gradient across the pulmonic valve of >64 mmHg (mean gradient >35 mmHg, Doppler jet velocity >4 m/s); moderate PS correlates with a peak gradient of 36–64 mmHg (Doppler jet velocity 3–4 m/s). Mild PS is characterized by a jet velocity <3 m/s (peak gradient <36 mmHg). PS rarely progresses in patients with mild PS but may worsen with age in those with moderate disease due to valve thickening and calcification. The right atrial (RA) *a* wave elevates in relation to the higher pressures needed to fill a noncompliant, hypertrophied RV. A prominent RA *v* wave signifies functional tricuspid regurgitation (TR) from RV and annular dilation. The CO is maintained until late in the course of the disease.

■ SYMPTOMS

Patients with mild or even moderate PS are usually asymptomatic and first come to medical attention because of a heart murmur (or early systolic click) that leads to echocardiography. With severe PS, patients may report exertional dyspnea or early-onset fatigue. Anginal chest pain from RV oxygen supply-demand mismatch and syncope may occur with very severe forms of obstruction, particularly in the presence of a destabilizing trigger such as atrial fibrillation, fever, infection, anemia, or pregnancy.

■ PHYSICAL FINDINGS

The murmur of mild or moderate PS is mid-systolic in timing, crescendo-decrescendo in configuration, heard best in the left second interspace, and usually introduced by an ejection sound (click) in younger adults whose valves are still pliable. The ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. This phenomenon reflects premature opening of the pulmonic valve by the elevated RV end-diastolic (post-atrial *a* wave) pressure. The systolic murmur increases in intensity during inspiration. With progressively severe PS, the ejection sound moves closer to the first heart sound and eventually becomes inaudible. A right-sided fourth heart sound may emerge. The systolic murmur peaks later and may persist through the aortic component of the second heart sound (*A*₂). Pulmonic valve closure is delayed, and the pulmonic component of the second heart sound (*P*₂) is reduced or absent. A prominent *a* wave, indicative of the higher atrial pressure necessary to fill the noncompliant RV, may be seen in the jugular venous pulse. A parasternal or RV lift can be felt with significant pressure overload. Signs of right heart failure due to RV systolic dysfunction, such as

TABLE 278-1 Causes of Pulmonic Valve Disease

VALVE LESION	ETIOLOGIES
Pulmonic stenosis	Congenital Carcinoid Tumor Endocarditis
Pulmonic regurgitation	Primary valve disease Congenital Post-valvotomy Endocarditis Carcinoid Annular enlargement Pulmonary hypertension Idiopathic dilation Marfan syndrome

hepatomegaly, ascites, and edema, are uncommon but may appear very late in the disease.

■ LABORATORY EXAMINATION

The electrocardiogram (ECG) will show right axis deviation, RVH, and RA enlargement in adult patients with severe PS. Chest x-ray findings include poststenotic dilation of the main PA in the frontal plane projection and filling of the retrosternal airspace due to RV enlargement on the lateral film. In some patients with RVH, the cardiac apex appears to be lifted off the left hemidiaphragm. The RA may also be enlarged. Transthoracic echocardiography (TTE) allows definitive diagnosis and characterization in most cases, with depiction of the valve and assessment of the jet velocity, gradient, RV function, PA pressures (which should be low), and any associated cardiac lesions. Transesophageal echocardiography (TEE) may be useful in some patients for improved delineation of the RV outflow tract (RVOT) and assessment of infundibular hypertrophy. Cardiac catheterization is not usually necessary for diagnostic purposes, but if performed, pressures should be obtained from just below and above the pulmonic valve with attention to the possibility that a dynamic component to the gradient may exist. The correlation between Doppler assessment of peak instantaneous gradient and catheterization-measured peak-to-peak gradient is weak. The latter may correlate better with the Doppler mean gradient.

TREATMENT**Pulmonic Stenosis**

Diuretics can be used to treat symptoms and signs of right heart failure. Provided there is less than moderate pulmonic regurgitation (PR), percutaneous pulmonic balloon valvuloplasty is recommended for symptomatic patients with moderate or severe PS and for asymptomatic patients with a peak gradient >64 mmHg (or mean gradient >35 mmHg). Surgery may be required when the valve is dysplastic (as seen in patients with Noonan's syndrome and other disorders). A multidisciplinary heart team is best positioned to make treatment decisions of this nature.

PULMONIC REGURGITATION

PR may develop as a consequence of primary valve pathology, annular enlargement, or their combination; after surgical treatment of RVOT obstruction in children with such disorders as tetralogy of Fallot; or after percutaneous pulmonic balloon valvotomy (Table 278-1). Carcinoid usually causes mixed pulmonic valve disease with PR and PS. Long-standing severe PA hypertension from any cause can result in dilation of the pulmonic valve ring and PR. Trace or mild PR of no hemodynamic or clinical consequence is frequently observed on TTE in the absence of structural pulmonic valve disease (Fig. 278-1).

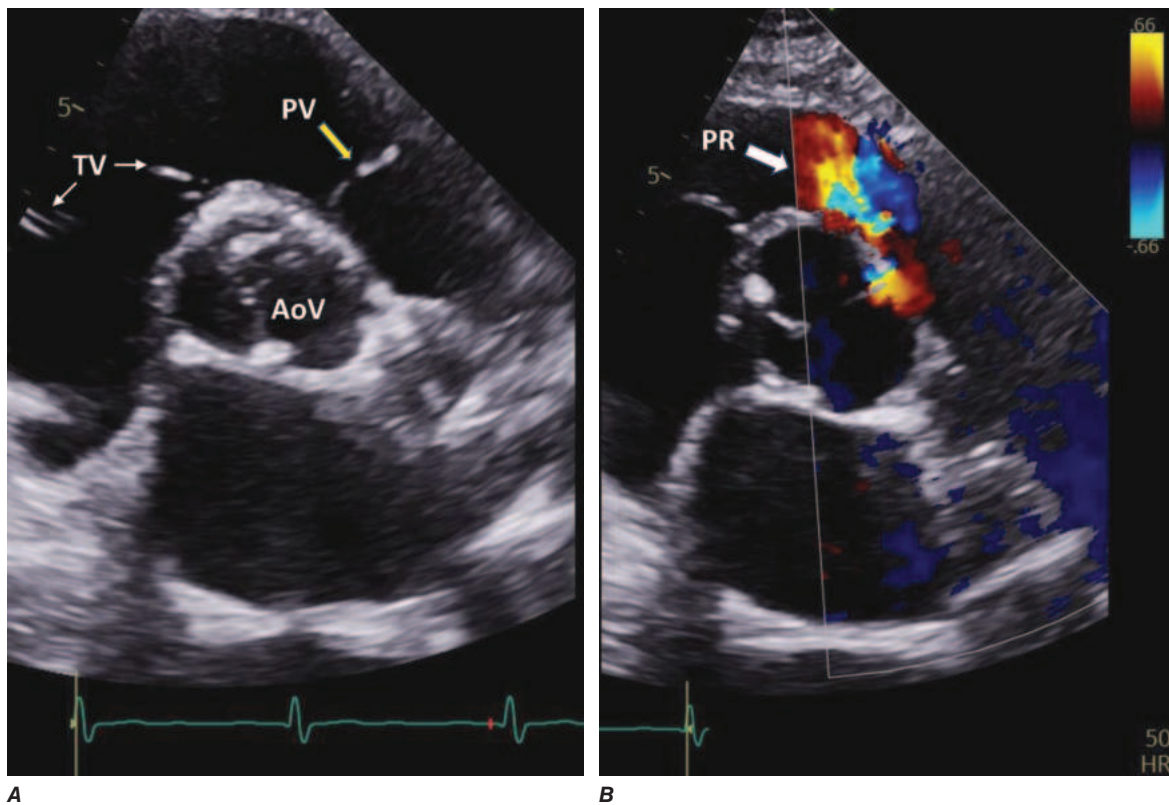


FIGURE 278-1 Pulmonic regurgitation. **A.** Transthoracic short axis window at the level of the aortic valve (AoV). The pulmonic valve (PV) is shown with the yellow arrow. Tricuspid valve (TV) leaflets are partially visualized (white arrows). **B.** Color flow Doppler image shows moderate pulmonic regurgitation (PR, white arrow).

■ PATHOPHYSIOLOGY

Severe PR results in RV chamber enlargement and eccentric hypertrophy. As is the case for aortic regurgitation (AR), PR is a state of increased preload and afterload. The diastolic pressure gradient between the PA to the RV, which drives the PR, progressively decreases throughout diastole and accounts for the decrescendo nature of the murmur. As RV diastolic pressure increases, the murmur becomes shorter in duration. The forward CO is preserved during the early stages of the disease but may not increase normally with exercise and declines over time. A reduction in RV ejection fraction may be an early indicator of hemodynamic compromise. In advanced stages, there is significant enlargement of the RV and RA with marked elevation of the jugular venous pressure.

■ SYMPTOMS

Mild or moderate degrees of PR do not, by themselves, result in symptoms. Other issues, such as PA hypertension, may dominate the clinical picture. With progressively severe PR and RV dysfunction, fatigue, exertional dyspnea, abdominal fullness/bloating, and lower extremity swelling may be reported.

■ PHYSICAL FINDINGS

The physical examination hallmark of PR is a high-pitched, decrescendo diastolic murmur (Graham Steell murmur) heard along the left sternal border that can be difficult to distinguish from the more frequently appreciated murmur of AR. The Graham Steell murmur may become louder with inspiration and is usually associated with a loud and sometimes palpable P_2 and an RV lift, as would be expected in patients with significant PA hypertension of any cause. Survivors of childhood surgery for tetralogy of Fallot or PS/pulmonary atresia may have an RV-PA conduit that is freely regurgitant because it does not contain a valve. PA pressures in these individuals are not elevated, and the diastolic murmur can be misleadingly low pitched and of short duration despite significant degrees of PR and RV volume overload.

■ LABORATORY EXAMINATION

Depending on both the etiology and severity of PR, the ECG may show findings of RVH and RA enlargement. On chest x-ray, the RV and RA

may be enlarged. Pulmonic valve morphology and function can be assessed with transthoracic Doppler echocardiography. RV systolic pressure can be estimated from the tricuspid valve systolic jet velocity. Cardiac magnetic resonance (CMR) imaging can provide greater anatomic detail, particularly in patients with repaired congenital heart disease, and more precise assessment of RV volumes and function. Cardiac catheterization is not routinely necessary but would be performed as part of a planned transcatheter PV procedure.

TREATMENT

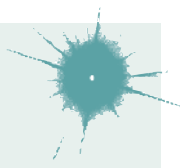
Pulmonic Regurgitation

In patients with significant functional PR due to PA hypertension and annular dilation, efforts to reduce pulmonary vascular resistance and pressure should be pursued. Such efforts may include pharmacologic/vasodilator and/or surgical/interventional strategies, depending on the cause of the PA hypertension (e.g., idiopathic PA hypertension, left-sided heart valve disease). Diuretics can be used to treat the manifestations of right heart failure. Surgical valve replacement for primary, severe, pulmonic valve disease, such as carcinoid or endocarditis, is rarely undertaken. Transcatheter pulmonic valve replacement has been successfully performed in many patients with severe PR after childhood repair of tetralogy of Fallot or pulmonic valve stenosis or atresia. This procedure was introduced clinically prior to transcatheter aortic valve replacement. Earlier concerns regarding an excess hazard of infective endocarditis with first-generation valves have led to procedural modifications.

■ FURTHER READING

OTTO CM et al: 2020 AHA/ACC guideline for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 143:e72, 2021.

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Many acquired and congenital cardiac lesions may result in stenosis and/or regurgitation of one or more heart valves. For example, rheumatic heart disease can involve the mitral (mitral stenosis [MS], mitral regurgitation [MR], or MS and MR), aortic (aortic stenosis [AS], aortic regurgitation [AR], or AS and AR), and tricuspid (tricuspid stenosis [TS], tricuspid regurgitation [TR], or TS and TR) valve, alone or in combination. The common association of functional TR with significant mitral valve disease is discussed in [Chap. 277](#). Severe mitral annular calcification can result in regurgitation (due to decreased annular shortening during systole) and mild or moderate stenosis (caused by extension of the calcification onto the leaflets resulting in restricted valve opening). Patients with severe AS and left ventricular (LV) remodeling may develop functional MR that may not improve after isolated aortic valve replacement (AVR). Primary MR due to mitral valve prolapse or chordal rupture has been noted in patients with severe AS. Aortic valve infective endocarditis (IE) may secondarily involve the mitral apparatus either by abscess formation and contiguous spread via the intervalvular fibrosa or by “drop metastases” from the aortic leaflets onto the anterior leaflet of the mitral valve. Mediastinal radiation may result in aortic, mitral, and even tricuspid valve disease, most often with mixed stenosis and regurgitation. Carcinoid heart disease may cause mixed lesions of either or both the tricuspid and pulmonic valves. Ergotamines, and the previously used combination of fenfluramine and phentermine, can rarely result in mixed lesions of the aortic and/or mitral valve. Patients with Marfan syndrome may have both AR from aortic root dilation and MR due to mitral valve prolapse (MVP). Myxomatous degeneration causing prolapse of multiple valves (mitral, aortic, tricuspid) can also occur in the absence of an identifiable connective tissue disorder. Bicuspid aortic or pulmonic valve disease can result in mixed stenosis and regurgitation. The former is also associated with aortic aneurysm disease and a predisposition to aortic dissection.

■ PATHOPHYSIOLOGY

In patients with multivalvular heart disease, the pathophysiologic derangements associated with the more proximal valve disease can mask the full expression of the attributes of the more distal valve lesion. For example, in patients with rheumatic mitral and aortic valve disease, the reduction in cardiac output (CO) imposed by the mitral valve disease will decrease the magnitude of the hemodynamic derangements related to the severity of the aortic valve lesion (stenotic, regurgitant, or both). Alternatively, the development of atrial fibrillation (AF) during the course of MS can lead to sudden worsening in a patient whose aortic valve disease was not previously felt to be significant. The development of reactive pulmonary vascular disease, sometimes referred to as a “secondary obstructive lesion in series,” can impose an additional challenge in these settings. As CO falls with progressive tricuspid valve disease, the severity of any associated mitral or aortic disease can be underestimated.

One of the most common examples of multivalve disease is that of functional TR in the setting of significant mitral valve disease. Functional TR occurs as a consequence of right ventricular and annular dilation; pulmonary artery (PA) hypertension may be present. The tricuspid leaflets are morphologically normal. Progressive degrees of TR lead to right ventricular volume overload and continued chamber and annular dilation. The TR is usually central in origin; reflux into the right atrium (RA) is expressed as large, systolic *c-v* waves in the RA pressure pulse. The height of the *c-v* wave is dependent on RA compliance and the volume of regurgitant flow. The RA waveform may become “ventricularized” in advanced stages of chronic, severe TR. CO falls and the severity of the associated mitral valve disease may become

more difficult to appreciate. Findings related to advanced right heart failure (e.g., ascites, edema) predominate. Primary rheumatic tricuspid valve disease may occur with rheumatic mitral disease and cause hemodynamic changes reflective of TR, TS, or their combination. With TS, the γ descent in the RA pressure pulse is prolonged. Typically, however, findings related to the mitral valve disease predominate over those related to the tricuspid valve disease.

Another example of rheumatic, multivalve disease involves the combination of mitral and aortic valve pathology, frequently characterized by MS and AR. In isolated MS, LV preload and diastolic pressure are reduced as a function of the severity of inflow obstruction. With concomitant AR, however, LV filling is enhanced and diastolic pressure may rise depending on the compliance characteristics of the chamber. Because the CO falls with progressive degrees of MS, transaortic valve flows will decline, masking the potential severity of the aortic valve lesion (AR, AS, or its combination). As noted above, onset of AF in such patients can be especially deleterious. The loss of atrial systole with AF may result in a critical reduction in CO, a rise in left atrial (LA) and LV diastolic pressures, and a further deleterious increase in heart rate.

Secondary (functional) MR may complicate the course of some patients with severe AS. The mitral valve leaflets and chordae tendineae are usually normal. Incompetence is related to changes in LV geometry (remodeling) and abnormal systolic tethering of the leaflets in the context of markedly elevated LV systolic pressures. Relief of the excess afterload with surgical or transcatheter AVR may result in reduction of the secondary MR. Persistence of significant, secondary MR following AVR is associated with impaired functional outcomes and reduced survival. Identification of patients who would benefit from concomitant treatment of their secondary MR at time of AVR is quite challenging. Most surgeons perform mitral valve repair of moderate-to-severe or severe secondary MR at time of surgical AVR. Significant primary MR may also coexist with AS and is routinely managed with repair (or replacement) at the time of AVR. There is increasing experience with the combination of transcatheter aortic valve implantation (TAVI) and transcatheter edge-to-edge mitral valve repair (TEER) in high surgical risk patients with severe AS and moderate-severe primary or secondary MR. Decision-making regarding the need for mitral valve intervention can be challenging.

In patients with mixed AS and AR, assessment of valve stenosis can be influenced by the magnitude of the regurgitant valve flow. Because transvalvular systolic flow velocities are augmented in patients with AR and preserved LV systolic function, the LV-aortic Doppler-derived pressure gradient and the intensity of the systolic murmur will be elevated to values higher than expected for the true systolic valve orifice size as measured by planimetry. Uncorrected, the Gorlin formula, which relies on forward CO (systolic transvalvular flow) and the mean pressure gradient for calculation of valve area, is not accurate in the setting of mixed aortic valve disease. Similar considerations apply to patients with mixed mitral valve disease. The peak mitral valve Doppler E wave velocity (v_p) is increased in the setting of severe MR because of enhanced early diastolic flow and may not accurately reflect the contribution to LA hypertension from any associated MS. When either AR or MR is the dominant lesion in patients with mixed aortic or mitral valve disease, respectively, the LV is dilated. When AS or MS predominates, LV chamber size will be normal or small. It can sometimes be difficult to ascertain whether stenosis or regurgitation is the dominant lesion in patients with mixed valve disease, although an integrated clinical and noninvasive assessment can usually provide clarification for purposes of patient management. For patients with moderate, mixed AS and AR in whom stenosis is the dominant lesion, the natural history tends to parallel what might be expected for isolated severe AS, and the treatment approach should be accordingly aligned.

Patients with significant AS, a nondilated LV chamber, and concentric hypertrophy will poorly tolerate the abrupt development of aortic regurgitation, as may occur, for example, with IE or after surgical AVR or TAVI complicated by paravalvular leakage. The noncompliant LV is not prepared to accommodate the sudden volume load, and as a result, LV diastolic pressure rises rapidly and severe heart failure develops.

Indeed, significant paravalvular regurgitation is a significant risk factor for short- to intermediate-term death following transcatheter AVR. Conditions in which the LV may not be able to dilate in response to chronic AR (or MR) include radiation heart disease, cardiac amyloid, and, in some patients, the cardiomyopathy associated with obesity and diabetes. Noncompliant ventricles of small chamber size predispose to earlier onset diastolic dysfunction and heart failure in response to any further perturbation in valve function.

■ SYMPTOMS

Compared with patients with isolated, single-lesion valve disease, patients with multiple or mixed valve disease may develop symptoms at a relatively earlier stage in the natural history of their disease. Symptoms such as exertional dyspnea and fatigue are usually related to elevated filling pressures, reduced CO, or their combination. Palpitations may signify AF and identify mitral valve disease as an important component of the clinical presentation, even when not previously suspected. Chest pain compatible with angina could reflect left or right ventricular oxygen supply/demand mismatch on a substrate of hypertrophy and pressure/volume overload with or without superimposed coronary artery disease. Symptoms related to right heart failure (abdominal fullness/bloating, edema) are late manifestations of advanced disease.

■ PHYSICAL FINDINGS

Mixed disease of a single valve is most often manifested by systolic and diastolic murmurs, each with the attributes expected for the valve in question. Thus, patients with AS and AR will have characteristic mid-systolic, crescendo-decrescendo and blowing, decrescendo diastolic murmurs at the base of the heart in the second right interspace and along the left sternal edge, respectively. Many patients with significant AR have mid-systolic outflow murmurs even in the absence of valve sclerosis/stenosis, and other findings of AS must be sought. The separate murmurs of AS and AR can occasionally be difficult to distinguish from the continuous murmurs associated with either a patent ductus arteriosus (PDA) or ruptured sinus of Valsalva aneurysm. With mixed aortic valve disease, the systolic murmur should end before, and not envelope or extend through, the second heart sound (S_2). The murmur associated with a PDA is heard best to the left of the upper sternum. The continuous murmur heard with a ruptured sinus of Valsalva aneurysm is often first appreciated after an episode of acute chest pain. An early ejection click, which usually defines bicuspid aortic valve disease in young adults, is often not present in patients with congenital mixed AS and AR. As noted above, both the intensity and duration of these separate murmurs can be influenced by a reduction in CO and transvalvular flow due to coexistent mitral valve disease or AF. In patients with isolated MS and MR, expected findings would include a blowing, holosystolic murmur and a mid-diastolic rumble (with or without an opening snap) best heard at the cardiac apex. An irregularly irregular heart rhythm in such patients would likely signify AF. Findings with TS and TR would mimic those of left-sided MS and MR, save for the expected changes in the murmurs with respiration. The murmurs of pulmonic stenosis and regurgitation behave in a fashion directionally similar to AS and AR; dynamic changes during respiration should be noted. Specific attributes of these cardiac murmurs are reviewed in [Chaps. 44 and 277](#).

■ LABORATORY EXAMINATION

The electrocardiogram (ECG) may show evidence of ventricular hypertrophy and/or atrial enlargement. ECG signs indicative of right-sided cardiac abnormalities in patients with left-sided valve lesions should prompt additional assessment for PA hypertension and/or right-sided valve disease. The presence of AF in patients with aortic valve disease may be a clue to the presence of previously unsuspected mitral valve disease in the appropriate context. The chest x-ray can be reviewed for evidence of cardiac chamber enlargement, valve and/or annular calcification, and any abnormalities in the appearance of the pulmonary vasculature. The latter could include enlargement of the main and proximal pulmonary arteries with PA hypertension and

pulmonary venous redistribution/engorgement or Kerley B lines with increasing degrees of LA and pulmonary venous hypertension. An enlarged azygos vein in the frontal projection indicates RA hypertension. Roentgenographic findings not expected based on a single or mixed valve lesion may reflect other valve disease.

Transthoracic echocardiography (TTE) is the most commonly used imaging modality for the diagnosis and characterization of multiple and/or mixed valvular heart disease and may often demonstrate findings not clinically suspected. Transesophageal echocardiography (TEE) may sometimes be required for more accurate assessment of valve anatomy (specifically, the mitral valve) and when IE is considered responsible for the clinical presentation. TTE findings of particular interest include those related to valve morphology and function, calcification, chamber size, ventricular wall thickness, biventricular function, estimated PA systolic pressure, and the dimensions of the great vessels, including the root and ascending aorta, PA, and inferior vena cava. Exercise testing (with or without echocardiography) can be useful when the degree of functional limitation reported by the patient is not adequately explained by the findings on TTE performed at rest. An integrated assessment of the clinical and TTE findings is needed to help determine the dominant valve lesion(s) and establish an appropriate plan for treatment and follow-up. Natural history is usually influenced to a relatively greater degree by the dominant lesion.

Cardiac magnetic resonance (CMR) imaging can be used to provide additional anatomic and physiologic information when echocardiography proves suboptimal but is less well suited to the evaluation of valve morphology. Cardiac computed tomography (CT) has been used to assess intracardiac structures in patients with complicated IE. It is invaluable in planning for transcatheter valve implantation. Coronary CT angiography provides a noninvasive alternative for the assessment of coronary artery anatomy prior to surgery or transcatheter intervention.

Invasive hemodynamic evaluation with right and left heart catheterization may be required to characterize more completely the individual contributions of each lesion in patients with either multiple or mixed valvular heart disease. It is strongly recommended when there is a discrepancy between the clinical and noninvasive findings in a symptomatic patient. Measurement of PA pressures and calculation of pulmonary vascular resistance (PVR) can help inform clinical decision-making in certain patient subsets, such as those with advanced mitral and tricuspid valve disease. It is important to identify any potential contribution to the clinical picture from pulmonary vascular disease. Attention to the accurate assessment of CO is essential. Coronary angiography (if indicated) can be performed as part of the procedure. Contrast ventriculography and great vessel angiography are performed infrequently.

TREATMENT

Multiple and Mixed Valve Disease

Management of patients with multiple or mixed valve disease can be challenging. As noted above, it is helpful to determine the dominant valve lesion and proceed according to the treatment and follow-up recommendations for it ([Chaps. 272–278](#)), being mindful of deviations from the expected course due to the contributions of more than one valve lesion. For example, AF that emerges in the course of moderate mitral valve disease may precipitate heart failure in patients with concomitant, severe aortic valve disease that was previously asymptomatic.

Medical therapies are limited and include diuretics when indicated for relief of congestion and anticoagulation to prevent stroke and thromboembolism in patients with AF. Blood pressure-lowering medications may be needed to treat systemic hypertension, which may aggravate left-sided regurgitant valve lesions, but should be initiated and titrated carefully. Pulmonary vasodilators to lower PVR are not generally effective in this context.

There is a paucity of evidence to inform practice guidelines for surgical and/or transcatheter valve intervention in patients with multiple or mixed valve disease. When there is a clear, dominant lesion, as for example in a patient with severe AS and mild AR, indications for intervention are straightforward and follow those recommended for patients with AS ([Chap. 272](#)). In other patients, however, there is less clarity, and decisions regarding intervention should be based on several considerations, including those related to lesion severity, ventricular remodeling, functional capacity, and PA pressures. In this regard, it is important to realize that patients with multiple and/or mixed valve disease may develop limiting symptoms or signs of physiologic impairment even with moderate valve lesions.

Concomitant aortic and mitral valve replacement surgery is associated with a significantly higher perioperative mortality risk than replacement of either valve alone; therefore, operation should be carefully considered. Double valve replacement surgery is usually performed for treatment of severe (unrepairable) valve disease at both locations and for the combination of severe disease at one location with moderate disease at the other to avoid the hazards of reoperation in the intermediate to late term for progressive disease of the unoperated valve. In addition, the presence of a prosthesis in the aortic position significantly restricts surgical exposure of the native mitral valve. The need for double valve replacement may also impact the decision regarding the type of prosthesis (i.e., mechanical vs tissue). In selected patients, TAVI for severe AS followed by edge-to-edge clip repair for severe MR can be accomplished during the same procedure.

Tricuspid valve repair for moderate or severe secondary (functional) TR at the time of left-sided valve surgery is now commonplace, particularly if there is dilation of the tricuspid annulus (>40 mm). The addition of tricuspid valve repair, consisting usually of insertion of an annuloplasty ring, adds little time or complexity to the procedure and is well tolerated, but may be associated with an excess risk of heart block and the need for a permanent pacemaker. Reoperation for repair (or replacement) of progressive TR years after initial surgery for left-sided valve disease, on the other hand, is associated with a relatively high perioperative mortality risk. Mitral valve repair or replacement for moderate or severe secondary MR at time of AVR for AS can usually be undertaken with acceptable risk for perioperative death or major complication.

The presence of moderate or severe MR in patients with rheumatic MS is a contraindication to percutaneous mitral balloon commissurotomy (PMBC). TAVI can be performed for mixed AS and AR when the anatomic findings related to annulus size, coronary height, and the distribution of calcium are favorable. Transcatheter management of both severe AS and severe primary or secondary MR (with deployment of an edge-to-edge clip) has been undertaken with increasing frequency in appropriately selected patients with prohibitive or high surgical risk. Further advances in transcatheter treatments for multiple and mixed valve disease are anticipated.

■ FURTHER READING

- ALAOUR B et al: Combined significant aortic stenosis and mitral regurgitation: Challenges in timing and type of intervention. *Can J Cardiol* 40:235, 2024.
- EGBE AC et al: Outcomes in moderate mixed aortic valve disease: Is it time for a paradigm shift? *J Am Coll Cardiol* 67:2321, 2016.
- GAMMIE JS et al: Concomitant tricuspid repair in patients with degenerative mitral regurgitation. *N Engl J Med* 286:327, 2022.
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280

Congenital Heart Disease in the Adult

Anne Marie Valente, Michael J. Landzberg

■ PREVALENCE

The number of adults with congenital heart disease (CHD) living in the United States is estimated to be at least 1.4 million. It is now projected that >10% of adults living with CHD in Europe will be over 60 years old by 2030. The majority of adults with CHD were diagnosed in childhood, although a substantial percentage may have CHD first recognized as adults. Lifelong follow-up in coordination with, or directly by, clinicians with expertise in adult congenital heart disease (ACHD) is recommended. In this chapter, we will review the current field of ACHD, with an introduction to CHD nomenclature and cardiac development. This is followed by a summary of the more common CHD lesions that may be diagnosed in adulthood. Lastly, some of the common repaired CHD lesions that are encountered in adults are discussed. Throughout the chapter, to aid in the understanding of congenital cardiac anatomy and physiology, we include figures displaying the passage of blood flow between blood vessels and cardiac chambers in various disorders ([Fig. 280-1](#)).

■ THE CHANGING LANDSCAPE OF ADULT CHD

A Relatively New Subspecialty in Cardiovascular Disease

Over the past two decades, the field of caring for adults with CHD has blossomed, and several nationwide initiatives have been initiated to standardize care. The American College of Cardiology and American Heart Association developed guidelines for the care of adults with CHD, first published in 2008 and revised in 2018, which emphasize the need for collaboration among primary care practitioners, cardiologists, and ACHD subspecialty cardiologists. The body of medical knowledge and competencies attendant with ACHD combined with skill acquisition in coordination of complex care over a patient's medical lifetime led in 2015 to ACHD board certification examinations by the American Board of Medical Subspecialties, as well as the establishment of requirements for advanced fellowship training in ACHD care by the Accreditation Council for Graduate Medical Education. In temporal association, the Adult Congenital Heart Association (ACHA) developed a process for ACHD care program accreditation based on standardization of infrastructural components felt requisite to achieve quality outcomes for ACHD.

■ SPECIAL CONSIDERATIONS FOR THE ACHD PATIENT

Due to the need for lifelong care, it is essential that pediatric cardiology programs partner with ACHD programs to provide successful transition of patients. However, gaps in care are common during transition, much of which may be due to disparities in social determinants of health, such as race, ethnicity, socioeconomic status, access to insurance, and residence in geographically remote locations. Additionally, adults with CHD may not recognize subtle changes in their exercise capacity, some of which are associated with worse survival; by the time symptoms are recognized, irreversible physiologic changes may have occurred. ACHD patients are, therefore, advised to undergo regular evaluations for surveillance of anatomic, hemodynamic, and electrophysiologic sequelae that may be present. In addition, specific situations may arise in which it is prudent to review care in consultation with an ACHD specialist, several of which are outlined below.

Noncardiac Surgery Nearly all adults with CHD can be classified with stage A (harboring risk) or greater degrees of heart failure. As such, adults with CHD may demonstrate limited hemodynamic reserve to altered myocardial perfusion or loading conditions and may have subclinical organ dysfunction that is not recognized by standard laboratory assessment. Comprehensive, multispecialty assessment and care strategy review are recommended in advance of invasive or

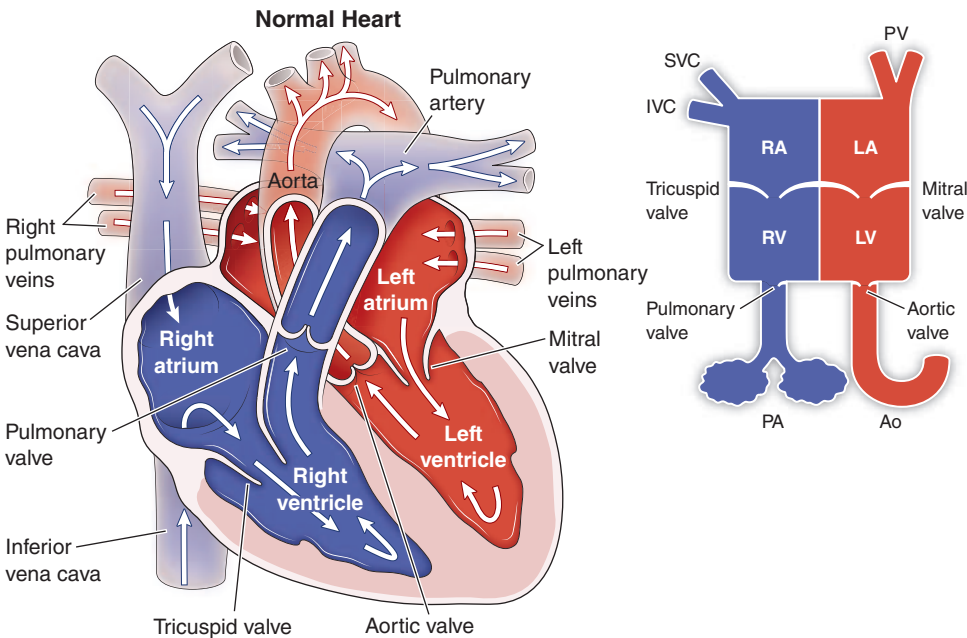


FIGURE 280-1 Normal heart. Understanding of congenital cardiac anatomy and physiology is facilitated by use of box diagrams, displaying passage of blood flow between blood vessels and cardiac chambers. Labeling (e.g., structure names, arrows to denote direction of flow, coloring to represent oxygen saturation, connections or obstructions, chamber or vascular pressures, oxygen saturations) can aid in representation. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

operative procedures for adults with CHD. **Figure 280-2** illustrates the multiorgan considerations that should be considered in adults with CHD during perioperative resuscitation and convalescence. Anesthetic management requires knowledge of anatomy, physiologic consequence of underlying defects, myocardial and vascular performance, presence and nature of previous palliative procedures and residual shunts, alteration of venous or arterial pathways within the circulation, and status of noncardiovascular organ physiology.

Pregnancy Women with CHD should receive counseling regarding both maternal and fetal risks prior to conceiving a pregnancy and should be cared for in institutions with experience in treating CHD during pregnancy. Preconception evaluation includes detailed medical history, with particular attention to the women's functional capacity, which is closely linked to maternal and fetal outcomes. **Table 280-1** lists the World Health Organization classification of risk during pregnancy in women with heart disease; women at risk should be strongly counseled about the significant risks of morbidity and mortality during pregnancy and the postpartum period. Normal physiologic hemodynamic changes of pregnancy are significant, occur over a relatively

condensed period of time, and may be compounded in adults with CHD. Silversides and colleagues have developed a weighted-risk score for pregnant women with heart disease, based on a large registry known as CARPREG 2. The highest-weighted risk factors (weight of 3 points) include a prior history of cardiac events or arrhythmias, decreased functional status (New York Heart Association class $\geq$ III), and presence of a mechanical heart valve. Risk factors that account for 2 points include ventricular dysfunction, high-risk left-sided valve disease/left ventricular outflow tract obstruction, pulmonary hypertension, coronary artery disease, and high-risk aortopathy. One point is assigned for late pregnancy assessment or no prior cardiac intervention. In this cohort, 16% of women experienced an adverse cardiac outcome, primarily heart failure and arrhythmia related. The predicted risks for cardiac events stratified according to point score were as follows: $\leq$ 1 point, 5%; 2 points, 10%; 3 points, 15%; 4 points, 22%; and $>$ 4 points, 41%.

Prepregnancy medications should be reviewed to ensure their safety in pregnancy. Alternatives to angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, direct oral anticoagulants, and endothelin receptor blockers should be considered, as these agents are teratogenic and contraindicated during pregnancy and should be discontinued. Women requiring anticoagulation must be advised of the challenges of managing anticoagulation during pregnancy, and individualized strategies should be developed. A fetal echocardiogram between 18 and 22 weeks of gestation is advised for patients with CHD. Additionally, both men and women with CHD should be counseled regarding the risk of CHD in their offspring.

■ CONGENITAL TERMINOLOGY, DEVELOPMENT, AND GENETICS

Congenital Nomenclature One of the challenges in caring for adults with CHD is the inconsistent terminology used to describe the congenital heart lesions. Several classification systems have been proposed, from the initial descriptions by Maude Abbott, Maurice Lev, and Jesse Edwards, to the extensive characterizations by Stella and Richard Van Praagh and Robert Anderson. In this chapter, we follow a segmental approach. The heart is composed of several segments that are

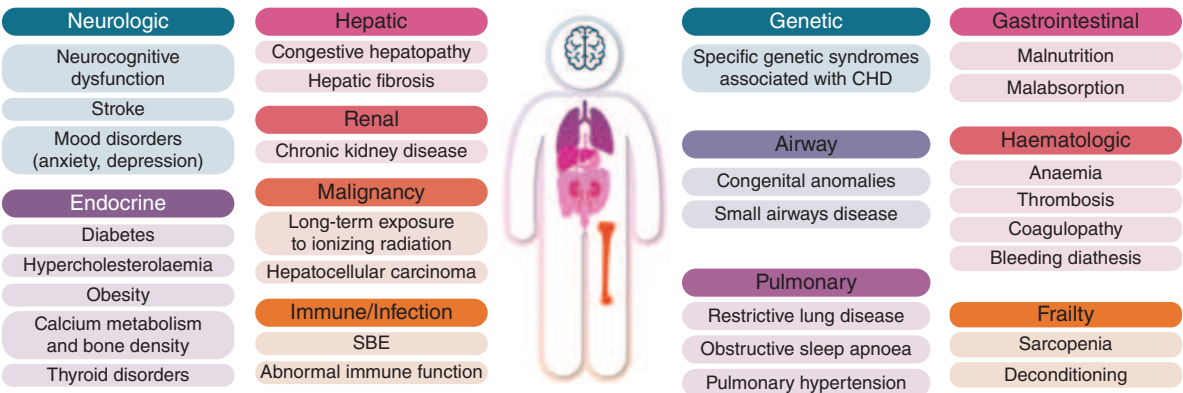


FIGURE 280-2 Noncardiac considerations in adults with congenital heart disease (CHD). SBE, subacute bacterial endocarditis. (Modified from J Buber et al: Common congenital heart problems in acute and intensive care. *Eur Heart J Acute Cardiovasc Care* 12:267, 2023.)

TABLE 280-1 Modified World Health Organization (mWHO) Classification of Heart Disease in Pregnancy

	mWHO I	mWHO II	mWHO II–III	mWHO III	mWHO IV
Diagnosis (if otherwise well and uncomplicated)	Small or mild Pulmonary stenosis Patent ductus arteriosus Mitral valve prolapse Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) Atrial or ventricular ectopic beats, isolated	Unoperated atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias (supraventricular arrhythmias) Turner syndrome without aortic dilatation	Mild left ventricular impairment (EF >45%) Hypertrophic cardiomyopathy Native or tissue valve disease not considered WHO I or IV (mild mitral stenosis, moderate aortic stenosis) Marfan or other HTAD syndrome without aortic dilatation Aorta <45 mm in bicuspid aortic valve pathology Repaired coarctation Atrioventricular septal defect	Moderate left ventricular impairment (EF 30–45%) Previous peripartum cardiomyopathy without any residual left ventricular impairment Mechanical valve Systemic right ventricle with good or mildly decreased ventricular function Fontan circulation Fontan circulation with good clinical course and without associated comorbidities Unrepaired cyanotic heart disease Other complex heart disease Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortic dilatation (40–45 mm in Marfan syndrome or other HTAD; 45–50 mm in bicuspid aortic valve, Turner syndrome ASI 20–25 mm/m ² , tetralogy of Fallot <50 mm) Ventricular tachycardia	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV) Previous peripartum cardiomyopathy with any residual left ventricular impairment Severe mitral stenosis Severe symptomatic aortic stenosis Systemic right ventricle with moderate or severely decreased ventricular function Severe aortic dilatation (>45 mm in Marfan syndrome or other HTAD, >50 mm in bicuspid aortic valve, Turner syndrome ASI >25 mm/m ² , tetralogy of Fallot >50 mm) Vascular Ehlers-Danlos Severe (re)coarctation Fontan with any complication
Risk	No detectable increased risk of maternal mortality and no/mild increased risk in morbidity	Small increased risk of maternal mortality or moderate increase in morbidity	Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity	Significantly increased risk of maternal mortality or severe morbidity	Extremely high risk of maternal mortality or severe morbidity

Abbreviations: ASI, aortic size index; EF, ejection fraction; HTAD, heritable thoracic aortic disease.

analyzed separately before formulating a comprehensive diagnosis. The principal segments are the atria, the ventricles, and the great arteries, which are joined together by the atrioventricular canal and the conus (infundibulum). In the normal heart, the right ventricle (RV) is right-sided and organized inflow-to-outflow from right to left, while the left ventricle (LV) is left-sided and organized inflow-to-outflow from left to right. It is important to determine the segmental alignments, that is, what drains into what. For example, in the normal heart, the right atrium (RA) is aligned with the RV and the LV with the aorta. Finally, the segmental connections, the way in which adjacent segments are physically linked to each other, are described. For example, in the normal heart, the pulmonary artery (PA) is connected to the RV by a complete muscular conus (infundibulum), while the aorta is connected to the LV by aortic-mitral fibrous continuity (without a complete conus). Alignment and connection are different concepts, and both are important, especially in complex defects.

Cardiac Development The heart starts to form in the third week of gestation and is nearly fully formed by 8 weeks' gestation. Mesodermal precardiac cells migrate to form the cardiac crescents (primary heart fields) in anterior lateral plate mesoderm, which are then brought together to form a primary linear heart tube by ventral closure of the embryo. Cells of the second heart field continue to proliferate outside the heart and are added to the heart tube over the course of embryogenesis, contributing to the atria, the RV, and outflow tract. Additionally, cardiac neural crest cells migrate into the developing heart in the 5th–6th weeks and are essential for septation of the outflow, formation of the semilunar valves, and patterning of the aortic arches. Once formed, the heart tube grows and elongates by addition of cells from the second heart field. The ends of the heart tube are relatively fixed by the pericardial sac so that as it elongates it must loop (bend), and in the vast majority of hearts, the loop falls to the right (D-loop). Further elongation pushes the mid-portion of the tube (future ventricles)

inferior or caudal to the inflow, resulting in the normal relationship between the atria and ventricles. Further growth pushes the outflow medially and is associated with outflow rotation, both processes essential for normal alignment of the outflow. Finally, the proximal part of the outflow is incorporated in the RV, shortening the outflow in association with further rotation. While this remodeling is occurring, the outflow is undergoing septation under the influence of cardiac neural crest cells. Septation proceeds from distal to proximal, culminating in formation and muscularization of the infundibular, or muscular, outflow septum, which inserts onto the superior endocardial cushion at the rightward rim of the outflow foramen, walling the aorta into the LV via the outflow foramen and the PA directly into the RV.

Genetic Considerations CHD is the most commonly occurring birth defect; etiologic contributors are increasingly recognized, although often speculated to be multifactorial. Children born with trisomy 21 have a 50% chance of having CHD, most commonly defects in the atrioventricular canal. Conotruncal defects are associated with several chromosomal abnormalities, most notably a deletion at chromosome 22q11 (DiGeorge syndrome). Echocardiographic clues to this association in patients with a conotruncal defect include an associated right aortic arch or aberrant subclavian artery. Many adults currently living with conotruncal defects may not have undergone testing for DiGeorge syndrome. This condition is important to recognize because a variety of psychiatric disorders and disabilities in cognitive function may be present and go untreated. Patients with Noonan syndrome commonly have a dysplastic pulmonary valve and have facial and lymphatic abnormalities. Several defects in specific genes have been associated with Noonan syndrome, most notably *PTPN11*. Adults with Williams syndrome (7q11.23 deletion) commonly have supravalvular aortic stenosis and diffuse arteriopathy, with a “cocktail-like” personality and hypercalcemia. There is a growing importance of genome-wide analyses in subjects with CHD.

TABLE 280-2 Congenital Etiologies of Right Heart Dilation

Congenital tricuspid valve disease
Tricuspid valve dysplasia with regurgitation
Ebstein anomaly
Congenital pulmonary valve regurgitation
Pulmonary arterial hypertension
Myocardial abnormalities
Arrhythmogenic RV cardiomyopathy
Uhl's anomaly
Shunt lesions
Partial anomalous pulmonary venous return
Primum ASD
Secundum ASD
Sinus venosus defect
Coronary sinus septal defect
Gerbode defect (LV-RA shunt)
Coronary artery fistula to the RA, CS
Postoperative residual shunts

Abbreviations: ASD, atrial septal defect; CS, coronary sinus; LV, left ventricle; RA, right atrium; RV, right ventricle.

SPECIFIC CHD LESIONS

Dilated Right Heart There are many congenital etiologies for right heart dilation (Table 280-2). These include congenital valvular anomalies (such as Ebstein anomaly or pulmonary regurgitation), intrinsic RV myocardial anomalies (arrhythmogenic RV dysplasia, Uhl's anomaly), or shunt lesions occurring proximal to the tricuspid valve (atrial septal defects or partial anomalous pulmonary veins). Cardiac imaging is critical in determining the etiology of right heart dilation, and knowledge of the anatomy and physiology of various shunt lesions is essential.

Atrial Septal Defect One of the most common etiologies of right heart dilation is presence of an atrial septal defect (ASD; Fig. 280-3A). Intracardiac communications allow blood transmission between chambers or spaces based on relative resistance, propulsion, and flow patterns. Patients with large ASDs often present in childhood; however, many ASDs are not discovered until adult life. The physiology of an ASD is predominantly that of a “left-to-right” shunt

(flow of pulmonary venous, or oxygenated, blood toward systemic venous, or deoxygenated, chambers or vessels). The degree of left-to-right shunting determines the amount of right heart volume loading and is dictated by the size of the defect as well as the diastolic properties of the heart. As patients age, several factors, such as diabetes mellitus, systemic hypertension, and atherosclerosis, may contribute to decreased compliance of the left-sided cardiac chambers and contribute to increased left-to-right shunting and symptomatology. The classic physical examination finding is a wide, fixed splitting of the second heart sound, which is due to prolonged RV ejection and increased PA capacitance, which, in turn, delay pulmonary valve closure. The surface electrocardiogram (ECG) commonly displays an incomplete right bundle branch block. Symptoms, when they occur, most commonly include exercise intolerance, arrhythmia, and dyspnea with exertion. It is not uncommon for adults to have incidentally noted asymptomatic ASD during evaluation of other comorbid issues. Right heart dilation, without additional etiology for such, in the setting of unrepaired ASD is considered a risk for progression toward symptomatic right heart failure, atrial arrhythmias, and potential development of pulmonary arterial hypertension (if such is not already present). Therefore, a patient with an ASD and right heart dilation, particularly with symptoms attributable to such, should be offered ASD closure. Pulmonary vascular disease leading to pulmonary hypertension develops in up to 10% of patients with unrepaired ASD, and Eisenmenger syndrome (ES) is a rare complication (see below). Management of patients with concomitant ASD and pulmonary hypertension should be coordinated with both ACHD and pulmonary hypertension experts.

Figure 280-3B illustrates the locations of various ASDs. The most common type of an ASD is a secundum ASD, which is a defect, or true deficiency in the atrial septum, in the region of the fossa ovalis. This should be differentiated from a patent foramen ovale (PFO), which is persistence of patency of the flap valve of the fossa ovalis (not associated with right-sided cardiac dilation) and persists in up to 25% of adults. Secundum ASDs can often be closed with occluder devices placed percutaneously. However, certain anatomic determinants make percutaneous closure less favorable, including large defects, inadequate tissue rims surrounding the defect, and concomitance of anomalous draining pulmonary veins. A primum ASD is a deficiency of the atrioventricular (AV) canal portion of the atrial septum; primum ASD is always associated with abnormal development of the AV valves,

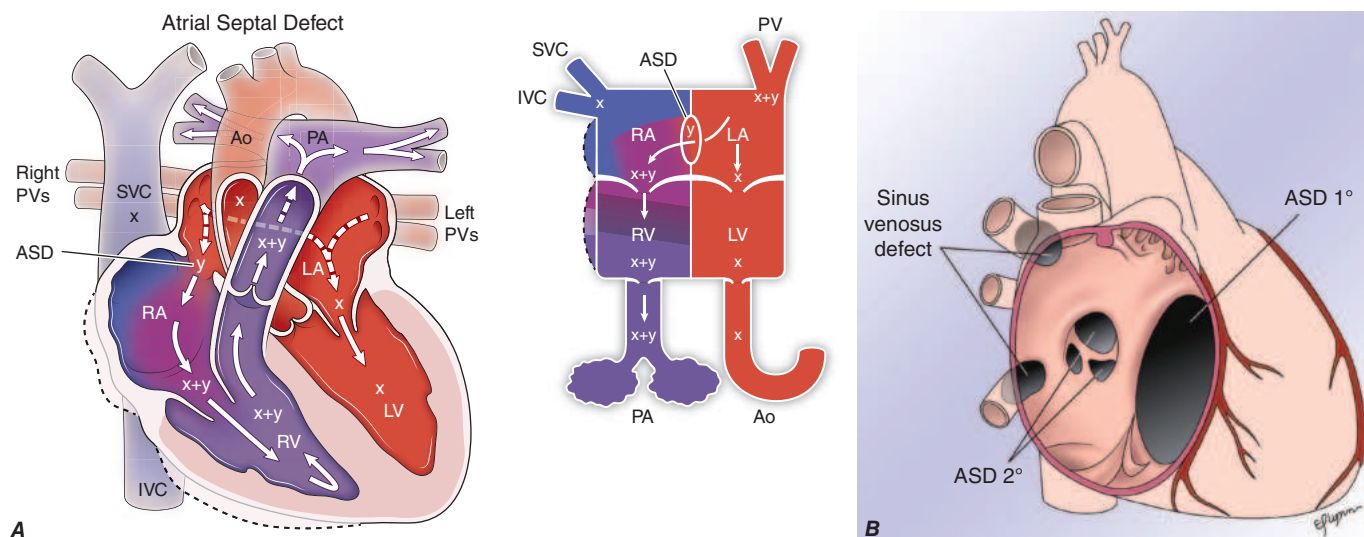


FIGURE 280-3 A. Atrial septal defect. In the presence of an atrial septal defect, the difference in compliance between the (RA + RV) as compared to the (LA + LV), combined with the size of the defect itself, allows for a “shunt” of flow (“y”) of “red” (oxygenated) blood from the left side of the heart to the right side (deoxygenated). Systemic venous return of pure deoxygenated blood (“x”) is increased by the oxygenated shunted blood (“y”) to increase volume of blood (“x + y”) in the RA, RV, and total blood flow to the lungs. If the volume or the sequelae of the shunted blood are sufficient, RA and RV can dilate (hashed lines), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; ASD, atrial septal defect; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava. **B.** Diagrammatic representation of the location of various atrial septal defects. ASD 1, primum atrial septal defect; ASD 2, secundum atrial septal defect. (Part B used with permission from Emily Flynn McIntosh, illustrator.)

most commonly resulting in a cleft in the mitral valve. A coronary sinus defect is rare and involves an opening between the coronary sinus and the left atrium. A sinus venosus defect is not a defect in the atrial septum but, rather, a defect between either the right superior vena caval-atrial junction and the right upper pulmonary vein(s) or, less commonly, the inferior vena caval-atrial junction and the right lower pulmonary veins. Surgical closure is required for primum ASDs, sinus venosus defects, and coronary sinus septal defects.

Partial Anomalous Pulmonary Venous Return Partial anomalous pulmonary venous return (PAPVR) is occasionally discovered in adults with right heart dilation or incidentally on cross-sectional imaging (Fig. 280-4). There are several possible anomalous connections, with the most common being a left upper pulmonary vein to an ascending vertical vein into the innominate vein or the right upper pulmonary vein draining to the superior vena cava. In the latter case, careful attention should be paid to ensure that there is not an associated sinus venosus defect. Concomitant pulmonary hypertension can occur but is uncommon. Symptomatology may be absent, and a decision to repair isolated PAPVR should include variance in anatomy, lung ventilation and perfusion, hemodynamic response to shunt, symptoms, and surgical experience.

Ebstein Anomaly Ebstein anomaly (Fig. 280-5) is the result of embryologic failure of delamination, or “peeling away,” of the tricuspid valve leaflets from the ventricular myocardium, resulting in adherence of the valve leaflets to the underlying myocardium. This results in a wide variety of abnormalities, including apical and posterior

Partial Anomalous Pulmonary Venous Return

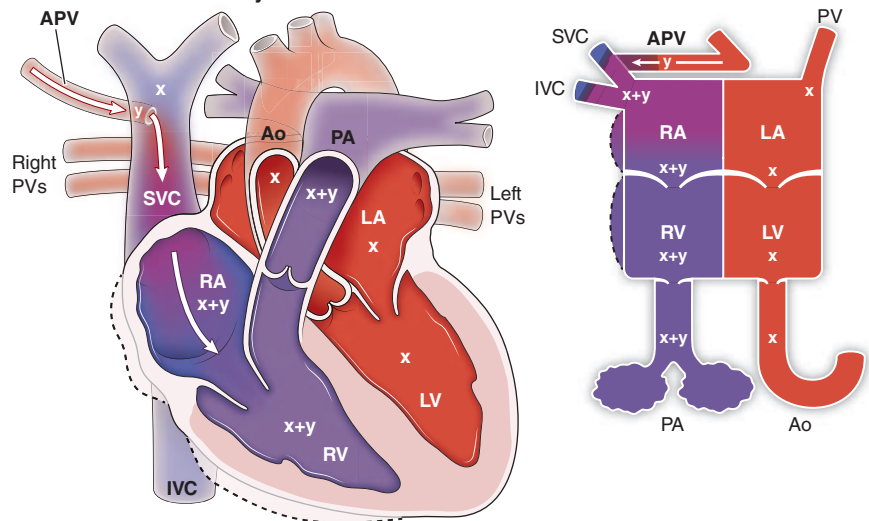


FIGURE 280-4 Partial anomalous pulmonary venous return. In the presence of an anomalously draining pulmonary vein (typically to a systemic vein such as the left innominate vein, SVC, or rarely IVC), an obligate “shunt” of flow (“y”) of “red” (oxygenated) blood from the affected pulmonary vein to the right heart (deoxygenated blood (“x”) ensues. Systemic venous return of pure deoxygenated blood (“x”) is increased by the oxygenated shunted blood (“y”) to increase volume of blood (“x + y”) in the SVC, RA, RV, and total blood flow to the lungs. If the volume or the sequelae of the shunted blood are sufficient, RA and RV can dilate (hashed lines), or shortness of breath can ensue. Ao, aorta; APV, anomalous pulmonary vein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

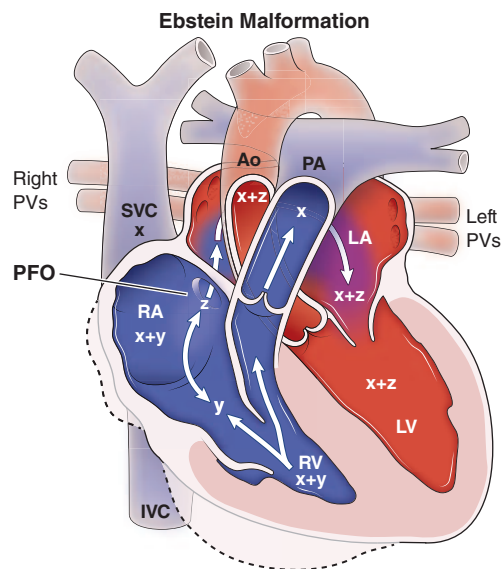


FIGURE 280-5 Ebstein malformation. In the presence of Ebstein anomaly, the tricuspid valve leaflets can be redundant, fenestrated, and sail-like (typically seen in the anterior leaflet*) or adherent to the underlying myocardium with apical displacement of the nonadherent components (typically the septal and posterior leaflets). Location and degree of leaflet coaptation are variable and account for varying degrees of tricuspid regurgitation, shift of the functional tricuspid valve anterior from the anatomic annulus into the right ventricle, “atrialization” of the right ventricle, and most commonly angulation of the tricuspid valve into the RV outflow tract. RA and RV dilation (hashed lines) can occur due to the effects of combined volume from systemic venous return (“x”) and tricuspid regurgitant flow (“y”). PFO is frequent; worsening compliance and elevation of pressure in the RA as compared to the LA can lead to increasing “right-to-left” (deoxygenated to oxygenated) shunt and cyanosis. RV myocardial function may be abnormal. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PFO, patent foramen ovale; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava; *, anterior tricuspid valve leaflet.

displacement of the dilated tricuspid valve annulus, dilation of the “atrialized” portion of the RV, and fenestrations, redundancy, and tethering typically of the anterior leaflet of the tricuspid valve. The malformed tricuspid valve is usually regurgitant but may occasionally be stenotic. The clinical presentation of Ebstein anomaly in the adult

depends on several factors, including the extent of tricuspid valve leaflet distortion, degree of tricuspid regurgitation (TR), right atrial pressure, and presence of an atrial level shunt. The physical examination of a patient with Ebstein anomaly may vary depending on the severity of disease. In more severe cases, the first heart sound may be split and the second component of the first heart sound may have a distinctive snapping quality (known as the sail sign, due to the redundancy of the anterior tricuspid valve leaflet). Patients with significant TR may have prominent “v” waves of the jugular venous pulsations; however, this finding is often absent due to abnormal right atrial compliance. The ECG is often abnormal, with right atrial and ventricular enlargement. Up to 20% of patients have evidence of ventricular pre-excitation (Wolff-Parkinson-White pattern). Surgical treatment includes a tricuspid valve repair or replacement, closure of any atrial level defects, and arrhythmia ablative procedures.

Shunt Lesions Causing Left Heart Dilation

Intracardiac shunts or intravascular passages that occur below the level of the tricuspid valve result in left heart dilation. The two major types of congenital shunts that result in left heart dilation are a ventricular septal defect (VSD; Fig. 280-6A) and patent ductus arteriosus (PDA; Fig. 280-7).

Ventricular Septal Defects VSDs are the most common congenital anomaly recognized at

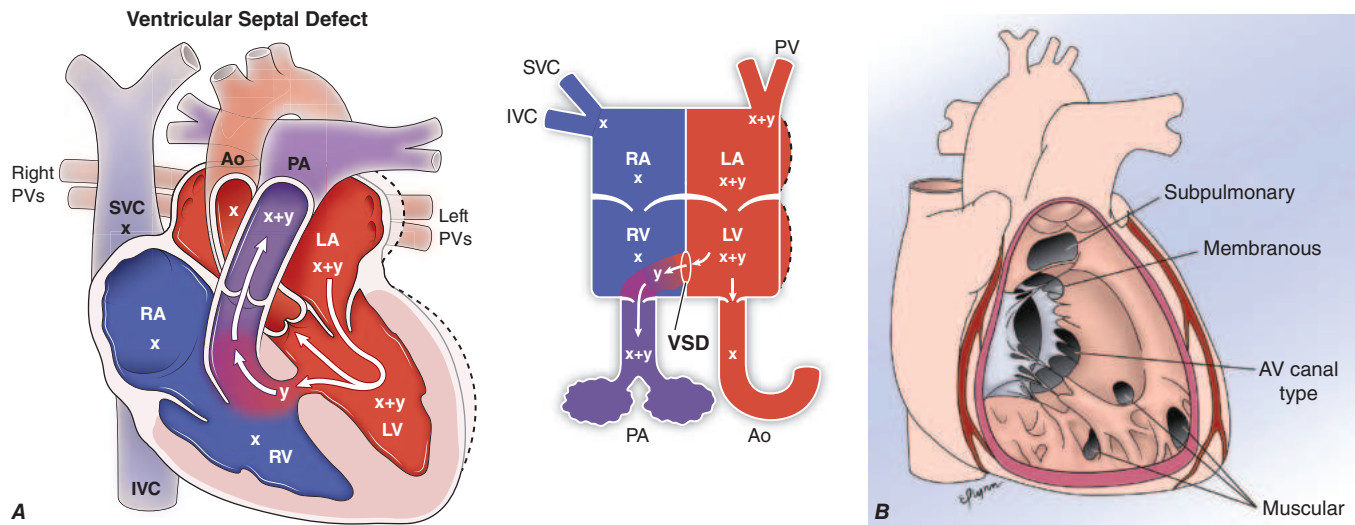


FIGURE 280-6 A. Ventricular septal defect. In the presence of a ventricular septal defect, the difference in pressure and outflow resistance in systole (and the difference in compliance in diastole) between the RV and LV, combined with the size of the defect itself, allow for a “shunt” of flow (“y”) of “red” (oxygenated) blood from the left side of the heart to the right side (deoxygenated). Systemic venous return of pure deoxygenated blood (“x”) is increased by the oxygenated shunted blood (“y”) to increase volume of blood (“x + y”) through the outflow of the RV into the lungs, and in the left atrium and left ventricle. If the volume or the sequelae of the shunted blood are sufficient, LA and LV can dilate (*hashed lines*), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava; VSD, ventricular septal defect. **B.** Diagrammatic representation of the location of various ventricular septal defects. AV, atrioventricular. (Part B used with permission from Emily Flynn McIntosh, illustrator.)

birth; however, they account for only ~10% of CHD in the adult, due to the high rate of spontaneous closure of small VSDs during the early years of life. Large VSDs usually cause symptoms of heart failure and poor somatic growth and are most often surgically closed before adulthood. Several classification systems for VSDs exist. **Figure 280-6B** illustrates various locations of VSDs; the most common location is in the membranous septum (also referred to as perimembranous or outlet defects). Muscular defects that persist into adult life are often pressure and flow restricted, resulting in no significant hemodynamic consequence. AV canal defects, also referred to as inlet defects, are located in the crux of the heart and are associated with abnormalities of the AV valve leaflets. Subpulmonary defects, also known as *conal septal defects*, are commonly associated with prolapse of the right coronary

cusp and aortic insufficiency. The outcome for adults with small VSDs without evidence of ventricular dilation or pulmonary hypertension is generally excellent.

Patent Ductus Arteriosus A PDA courses between the aortic isthmus and the origin of one of the branch PAs. Small PDAs are often silent to auscultation and do not cause hemodynamic changes. The classic murmur is heard best just below the left clavicle and typically extends from systole past the second heart sound into diastole, reflecting flow turbulence and gradient between the aorta and the PAs (resulting in left-to-right shunting). Large PDAs will lead to left heart dilation and may lead to chronically elevated pulmonary vascular resistance, including the potential for ES.

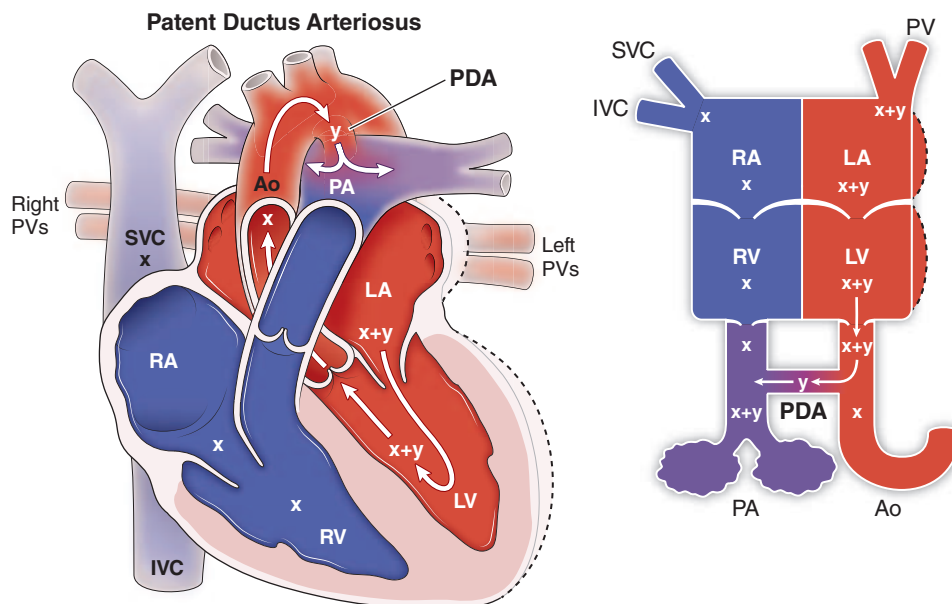


FIGURE 280-7 Patent ductus arteriosus. In the presence of a patent ductus arteriosus, the difference in pressure and resistance in both systole and diastole between the pulmonary arteries and the aorta, combined with the size of the ductus itself, allow for a “shunt” of flow (“y”) of “red” (oxygenated) blood from the aorta to the pulmonary arteries (deoxygenated). Systemic venous return of pure deoxygenated blood (“x”) is increased by the oxygenated shunted blood (“y”) to increase volume of blood (“x + y”) in the lungs, the left atrium, the left ventricle, and out the aortic valve. If the volume or the sequelae of the shunted blood are sufficient, LA and LV can dilate (*hashed lines*), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PDA, patent ductus arteriosus; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

MODERATE AND COMPLEX CHD

Tetralogy of Fallot Tetralogy of Fallot (TOF) is the most common form of cyanotic CHD, occurring in 0.5 per 1000 live births. It involves anterior deviation of the conal septum, resulting in RV outflow tract (RVOT) obstruction, a VSD, RV hypertrophy, and an overriding aorta (Fig. 280-8A, B). There is a large spectrum of severity of disease in TOF, from patients who have only mild pulmonary stenosis to those with complete pulmonary atresia (TOF/PA). Current surgical strategies involve primary repair in infancy (Fig. 280-8C); however, many adults

may have first undergone palliative procedures (Blalock-Taussig, Potts, Waterston shunts) prior to a complete repair. The goal of surgical repair is to alleviate the pulmonary stenosis and close the VSD. Up to 10% of patients with TOF have an anomalous coronary artery, most commonly, an anomalous left anterior descending coronary artery from the right coronary cusp. Patients with an anomalous coronary as well as those with TOF/PA may require an RV-to-PA conduit.

Adults with repaired TOF often have hemodynamic sequelae that may require reintervention in adulthood (Table 280-3). Pulmonary

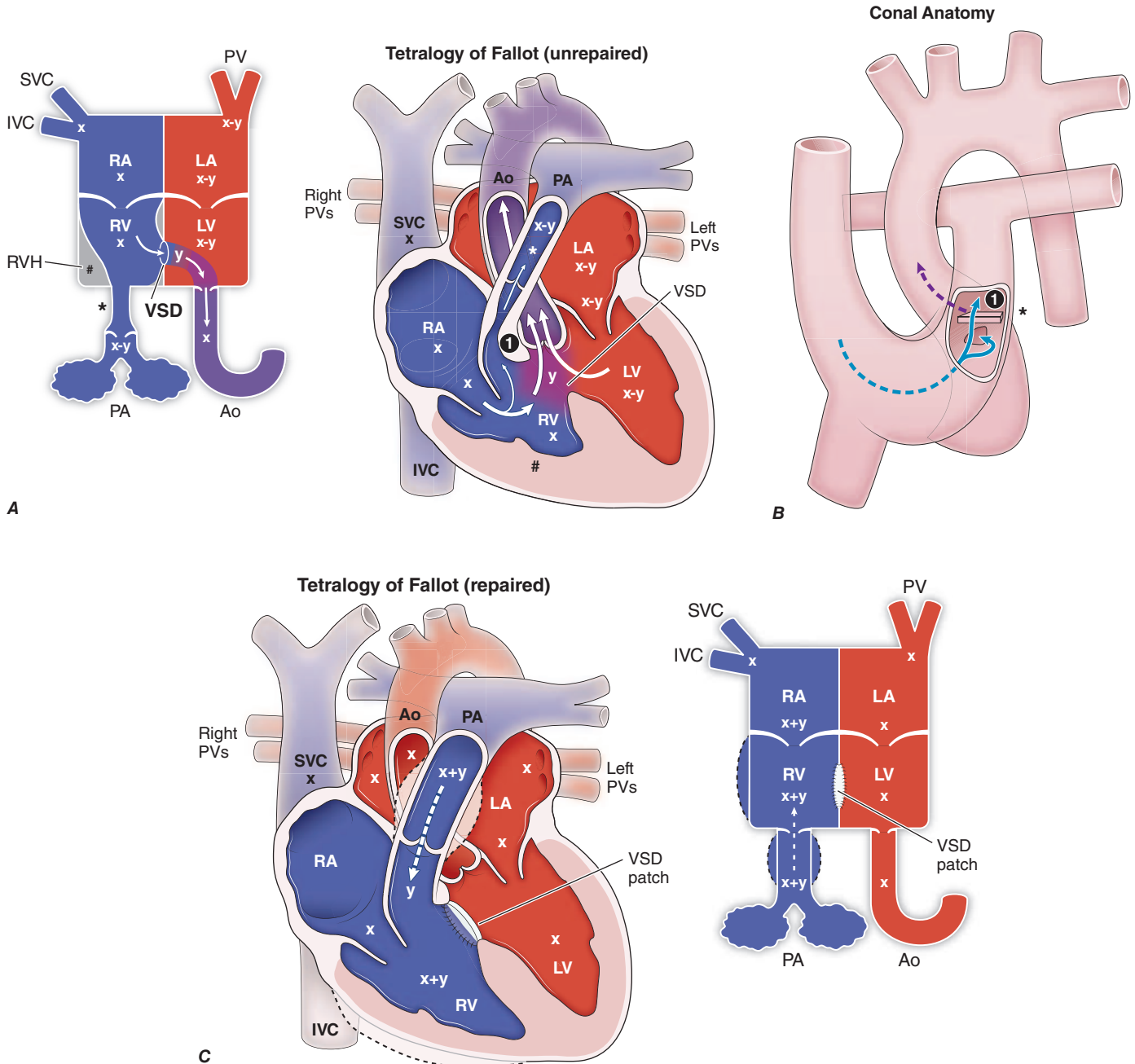


FIGURE 280-8 **A.** Tetralogy of Fallot involves anterior and superior malalignment of a bar of tissue (conal septum) (see * in part **B**, which presents a cut-away view through the anterior surface of the RV, into the RV outflow), partially obstructing the right ventricular outflow (under the pulmonary valve, i.e., “subpulmonary stenosis”; labeled as 1), and leaving a gap in the interventricular septum (VSD). The pulmonary valve annulus is typically hypoplastic. Outflow obstruction prevents regression of right ventricular hypertrophy (#), which was present in utero. The difference in pressure and outflow resistance in systole (and the difference in compliance in diastole) between the obstructed RV and the LV allows for a “shunt” of flow (“y”) of “blue” (deoxygenated) blood from the right side of the heart to the left side (oxygenated). Systemic venous return of pure deoxygenated blood (“x”) is decreased by the shunted blood (“y”), leading to a total decrease in the volume of blood (“x-y”) passing beyond into the lungs. The deoxygenated shunted blood (“y”) mixes with fully oxygenated blood in the LV, contributing to systemic arterial cyanosis. **C.** Tetralogy of Fallot—repaired. After modern repair of tetralogy of Fallot, VSD has been patched closed, and outflow tract obstruction has been surgically removed, frequently at the expense of a patch enlarging the pulmonary valve annulus at the expense of sacrificing the integrity of the pulmonary valve (causing pulmonary regurgitation). The pulmonary regurgitant volume (“y”) is added to systemic venous return (“x”), contributing to RV chamber enlargement (hashed lines) and may be associated with tricuspid annular dilation and valve regurgitation, resulting in RA enlargement. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; RVH, right ventricular hypertrophy; SVC, superior vena cava; VSD, ventricular septal defect.

TABLE 280-3 Potential Sequelae of Repaired Tetralogy of Fallot

Right atrial dilation
Right ventricular dilation
Right ventricular dysfunction
Right ventricular outflow tract obstruction
Pulmonary regurgitation
Branch pulmonary artery stenosis
Tricuspid regurgitation
Residual ventricular septal defect
Left ventricular dysfunction
Aortic root dilation
Atrial arrhythmias
Ventricular arrhythmias
Sudden cardiac death

regurgitation is common following TOF repair and is usually associated with RV dilation. Accurate quantification of RV size, function, and mass is particularly important in adults after repair of TOF, as RV dilation, dysfunction, and hypertrophy are associated with adverse outcomes in these patients. Patients may also have residual RVOT obstruction, which may occur beneath the pulmonary valve, at the valve level, above the valve, or in the branch PAs. Cardiac magnetic resonance imaging is routinely used in the surveillance of these patients. Left ventricular dysfunction is present in at least 20% of adults with repaired TOF, particularly those who were repaired later in life, had prior palliative shunts, or have concomitant RV dysfunction.

As patients age with repaired TOF, both atrial and ventricular arrhythmias occur with increasing frequency. A QRS duration on a

resting ECG of 180 ms or more has been associated with increased risk of ventricular tachycardia and sudden death in this patient population. In one prospective follow-up study of 144 adults with repaired TOF, there was a 72% survival at 40 years, but only a 25% cumulative event-free survival. These events include need for reintervention (most commonly pulmonary valve replacement [PVR]), symptomatic arrhythmias, and heart failure.

The most common reintervention in a repaired TOF patient is a PVR. However, optimal timing of PVR in asymptomatic patients with repaired TOF remains unclear. Traditionally, PVR has been accomplished with a surgical procedure; however, percutaneous implantation of pulmonary valves is becoming increasingly utilized in clinical practice.

Patients with repaired TOF may also undergo interventions including closure of residual VSDs, dilation and/or stenting of the RVOT or branch PAs, and tricuspid valve repair. Patients with clinically significant arrhythmias may benefit from catheter ablation.

Transposition of the Great Arteries Transposition of the great arteries (TGA) is defined by the great arteries arising from the opposite side of the ventricular septum than normal; as such, the aorta arises from the RV and the PA from the LV. The more common form of TGA, known as *D-loop* TGA, involves AV concordance and ventricular-arterial discordance, resulting in a physiology that allows two circuits to be in parallel rather than in series (**Fig. 280-9A**) and intense cyanosis shortly after birth. This physiology is not compatible with long-term survival without surgical intervention. Patients with TGA may be born with additional congenital defects (most commonly a VSD).

The surgical repairs for *D-loop* TGA have evolved over time. In the late 1950s through the 1970s, the atrial switch procedure (Mustard, Senning procedures) was performed (**Fig. 280-9B**). These atrial switch

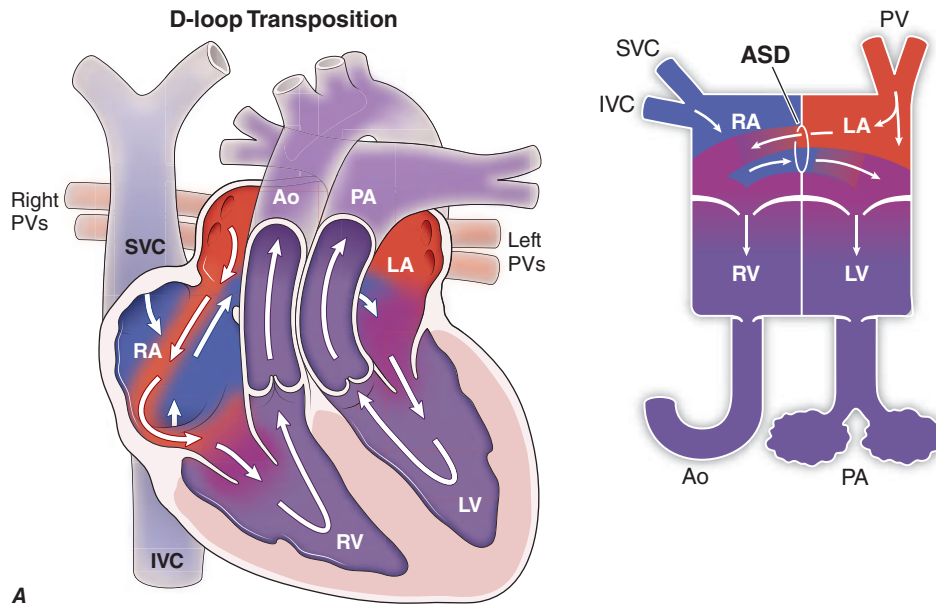


FIGURE 280-9 A. Transposition of the great arteries. When the great arteries are transposed, the aorta arises from the RV, and the pulmonary artery arises from the LV, leaving deoxygenated blood circulating from systemic veins to systemic arteries in separated fashion from oxygenated blood, which circulates from pulmonary veins to pulmonary arteries. Without interchamber or intravascular communications, this circulation is incompatible with life. Presence of an atrial septal defect (ASD), depicted here, ventricular septal defect (VSD), or patent ductus arteriosus (PDA) allows for some interchamber or intravascular mixing and, at best, partial relief of cyanosis and sustenance of life, at the expense of increased pulmonary blood flow. **B.** Atrial switch. Atrial level switch procedures (Mustard and Senning) were the first standardized surgeries to alter the natural course of complex congenital heart disease, utilizing intracardiac rerouting via a “baffle” to redirect blood flow. The atrial switch simulates inverted trousers, with each “pants leg” (*) attaching to either the SVC or the IVC, transporting deoxygenated blood through the interior of the trousers to the “waist of the trousers” and directing blood through the mitral valve to the LV and out the PA. Surgical removal of the atrial septum allows pulmonary venous return to traverse from posterior left atrium through the space between the pants legs of the baffle, through the tricuspid valve to the RV (serving as the “systemic ventricle,” i.e., that pumps to the systemic arterial circulation), through the aorta. Non-infrequent sequelae include sinus node dysfunction, atrial arrhythmias, systolic dysfunction of the RV, tricuspid regurgitation (from RV to LA), leaks in the baffle material allowing shunting of blood, and obstruction of the systemic or pulmonary venous baffles. **C.** Arterial switch. The arterial switch operation allowed both anatomic and physiologic correction for *D-loop* transposition of the great arteries. Successful surgical switching of the PA and the Ao above the level of the native roots (hashed lines) necessitated ability to transfer coronary artery origins contained within a button of tissue (*) back to the neo-aorta (now supported by the LV). Deoxygenated blood flow from SVC and IVC passes from RA to RV to PA, and oxygenated blood passes from PV to LA to LV to Ao. Uncommon sequelae include obstruction at any of the surgical sites (supravalvar PA or Ao stenosis, coronary orifice obstruction) or more distal obstructions due to tension placed on the PA, Ao, or coronary arteries. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

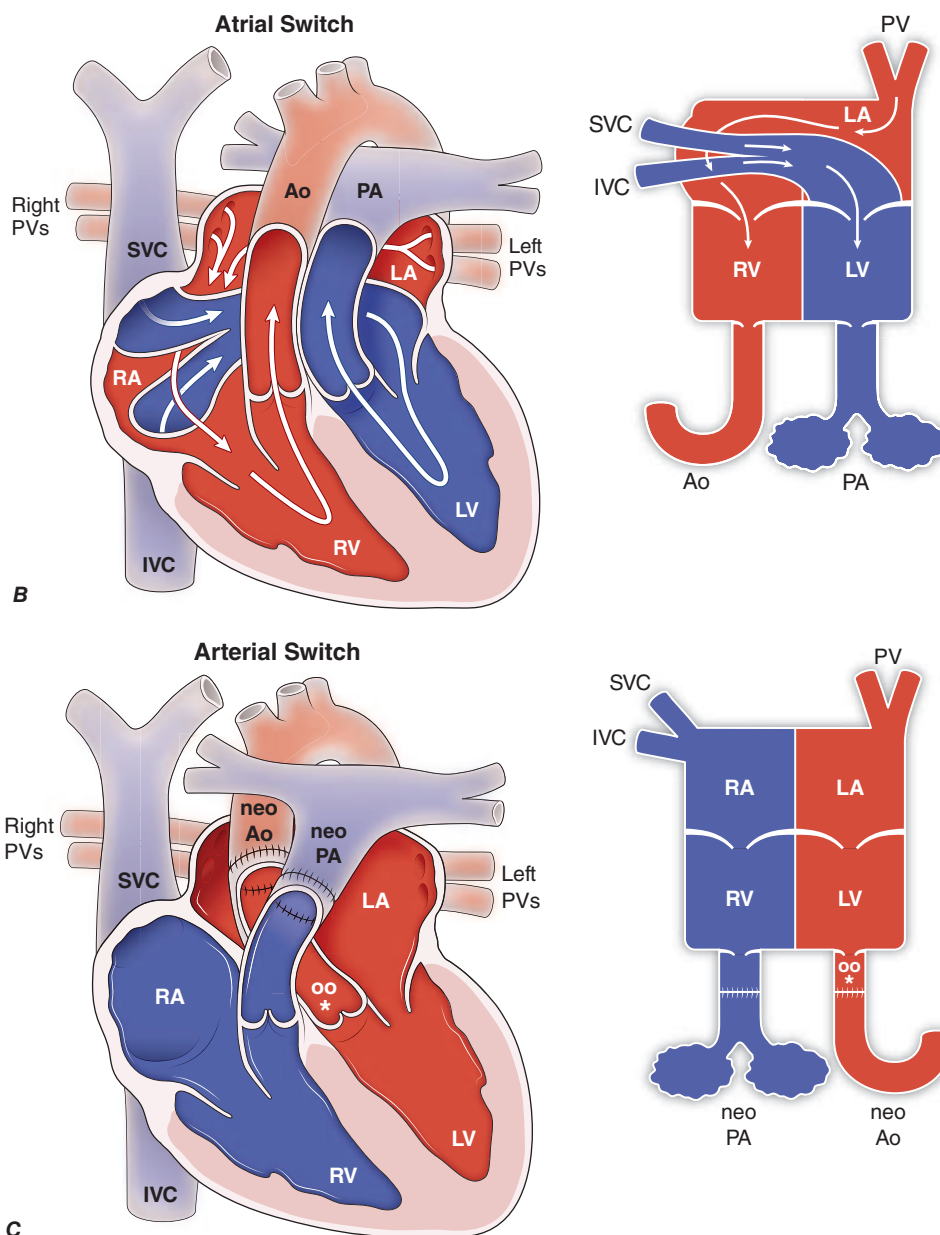


FIGURE 280-9 (Continued)

procedures relieved the cyanosis but left the patient with a systemic RV. Despite moderate-term survival over decades, there are multiple long-term sequelae that may present following the atrial switch procedure. The most worrisome complication is that of systemic RV dysfunction. The prevalence of RV dysfunction in this population is not well defined. Limited study has failed to reveal medical therapies effective for systemic RV dysfunction.

A subset of patients with D-loop TGA, VSD, and PS may have undergone a Rastelli procedure. This intervention involves placing an RV-to-PA conduit and routing the LV to the aorta through the VSD, which results in relief of cyanosis and the benefit of a systemic LV.

In the 1980s, the arterial switch operation (ASO; Fig. 280-9C) became the surgical procedure of choice for D-loop TGA. This procedure involves transecting the great arteries above the sinuses and placing the PAs anteriorly to come into alignment with the RV, resulting in draping of the branch PAs over the ascending aorta. A coronary artery translocation is performed. The ASO has resulted in substantial long-term survival.

The potential long-term sequelae of the various surgical procedures for D-loop TGA are listed in Table 280-4.

The less common form of TGA, known as *L-loop TGA* (physiologically corrected or “congenitally corrected” TGA; Fig. 280-10), may not require surgical intervention but is presented here in relation to other forms of TGA. L-loop TGA involves both AV discordance (RA allowing passage of deoxygenated systemic venous return to the LV, and

TABLE 280-4 Long-Term Sequelae of D-Loop TGA Surgery

ATRIAL SWITCH	ARTERIAL SWITCH	RASTELLI PROCEDURE
Systemic venous baffle	Arterial anastomosis stenosis	Subaortic stenosis
Pulmonary venous baffle	Branch PA stenosis	RV-PA conduit obstruction
RV (systemic) dysfunction	Neo-aortic root dilation	Pulmonary regurgitation
Tricuspid regurgitation	Neo-aortic regurgitation	Ventricular dysfunction
Baffle leaks	Coronary artery stenosis	
LVOT obstruction (PS)	LV dysfunction	

Abbreviations: LV, left ventricle; LVOT, left ventricular outflow tract; PA, pulmonary artery; PS, pulmonary stenosis; RV, right ventricle; TGA, transposition of the great arteries.

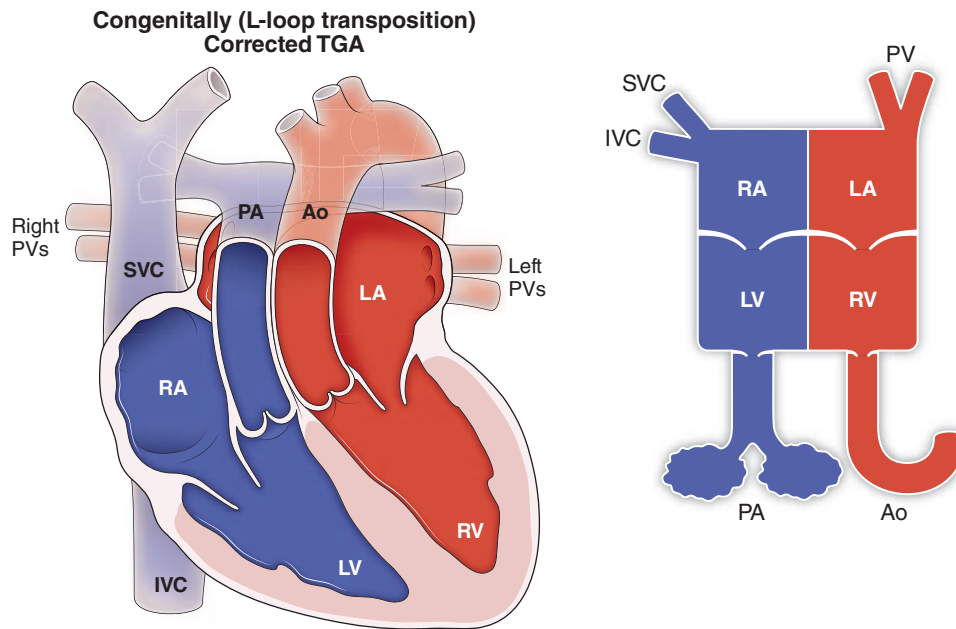


FIGURE 280-10 Congenitally corrected transposition of the great arteries. Physiologically corrected transposition of the great arteries (also known as *congenitally corrected transposition of the great arteries*) is characterized by atrioventricular discordance and ventriculoarterial discordance. Systemic venous blood passes from the right atrium (RA) through the mitral valve into the morphologic left ventricle (LV) to the pulmonary artery (PA). Oxygenated blood then returns to the lungs to the left atrium (LA) through the tricuspid valve into the morphologic right ventricle (RV) and then out the aorta (Ao). IVC, inferior vena cava; PV, pulmonary veins; SVC, superior vena cava.

conversely, the left atrium conducting oxygenated pulmonary venous blood to the RV) as well as ventriculoarterial discordance (connections of LV to PA, RV to aorta). This results in normal arterial oxygen saturation, yet an RV associated with the aorta. Patients with L-loop TGA commonly have associated congenital anomalies, including dextrocardia, ASDs, a dysplastic tricuspid valve, and pulmonary stenosis. Conduction disturbances are common, and complete heart block occurs in up to 30% of patients. Those patients without associated defects may not present until later in life, most commonly with heart failure, TR, or newly recognized conduction disease.

Coarctation of the Aorta Adults with coarctation of the aorta (**Fig. 280-11**) typically have a shelf-like obstruction at the level of the descending aorta that passes just posterior to the junction of the main and left PA; obstruction less commonly involves the transverse aortic arch. On physical examination, the lower extremity blood pressure and pulses are lower than (and delayed in timing, in contrast to) the upper extremity values, unless significant aortic collaterals have developed. A continuous murmur over the scapula may be present due to the collateral blood flow. Significant coarctation increases afterload to all proximal structures in the path of oxygenated blood, from LV and coronary arteries to ascending and transverse aorta, to cerebral and arm vessels and proximal descending aorta. Bicuspid aortic valve (typically with right-left commissural fusion) is a common association. In women with short stature, webbed neck, lymphedema, and primary amenorrhea, a concomitant diagnosis of Turner syndrome should be considered, the presence of which indicates greater degree of, and risks from, sequelae from seemingly similar anatomy and physiology. Patients who have undergone surgical repair in general have a good prognosis; however, they remain at risk for systemic hypertension, premature atherosclerosis, LV failure, and aortic aneurysm, dissection, and recurrent coarctation.

Single Ventricle The term *single ventricle heart disease* is imprecise but useful in some settings, as it refers to congenital heart conditions in which one ventricle or its valves preclude surgical creation of a biventricular circulation. Common congenital diagnoses in this category include tricuspid atresia, double inlet LV, and hypoplastic left heart syndrome. Most patients with single ventricle physiology undergo a series of surgeries culminating in a Fontan procedure (Fig. 280-12A, B). Since its initial use for tricuspid valve atresia in

1971, multiple modifications of this procedure have occurred, with common features of near complete separation of the pulmonary and systemic circulations. The Fontan procedure utilizes the single ventricle to pump pulmonary venous (oxygenated) blood through the aorta to the body and allows for "passive" flow of systemic venous return of deoxygenated blood through surgically created connections to the lungs. Patients who have undergone a Fontan procedure are at risk for multiple comorbidities in adulthood, including atrial arrhythmias, heart failure, renal and hepatic dysfunction, and both venous and arterial thrombosis and embolism.

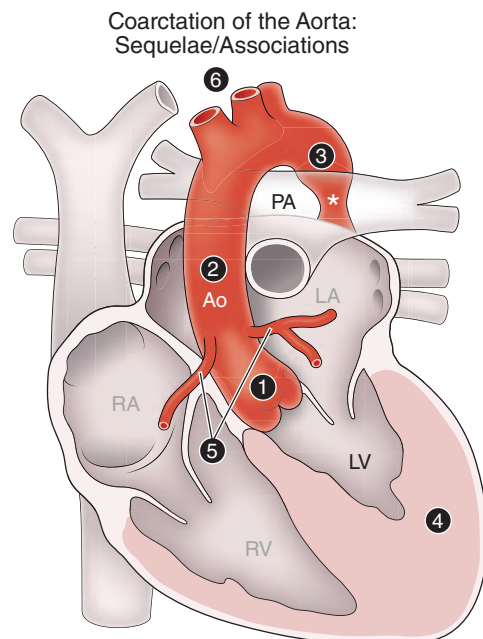


FIGURE 280-11 Aortic coarctation (*). Bicuspid aortic valve (1) is most common concomitant lesion. Sequelae from aortic coarctation (unrepaired or repaired) include systemic arterial hypertension, ascending (2) or descending (3) aortic enlargement or aneurysm formation, left ventricular (LV) hypertrophy (4), LV diastolic and systolic heart failure, accelerated coronary (5) or cerebral (6) atherosclerosis, cerebral aneurysm formation, and recurrence of coarctation after repair. Ao, aorta; PA, pulmonary arteries.

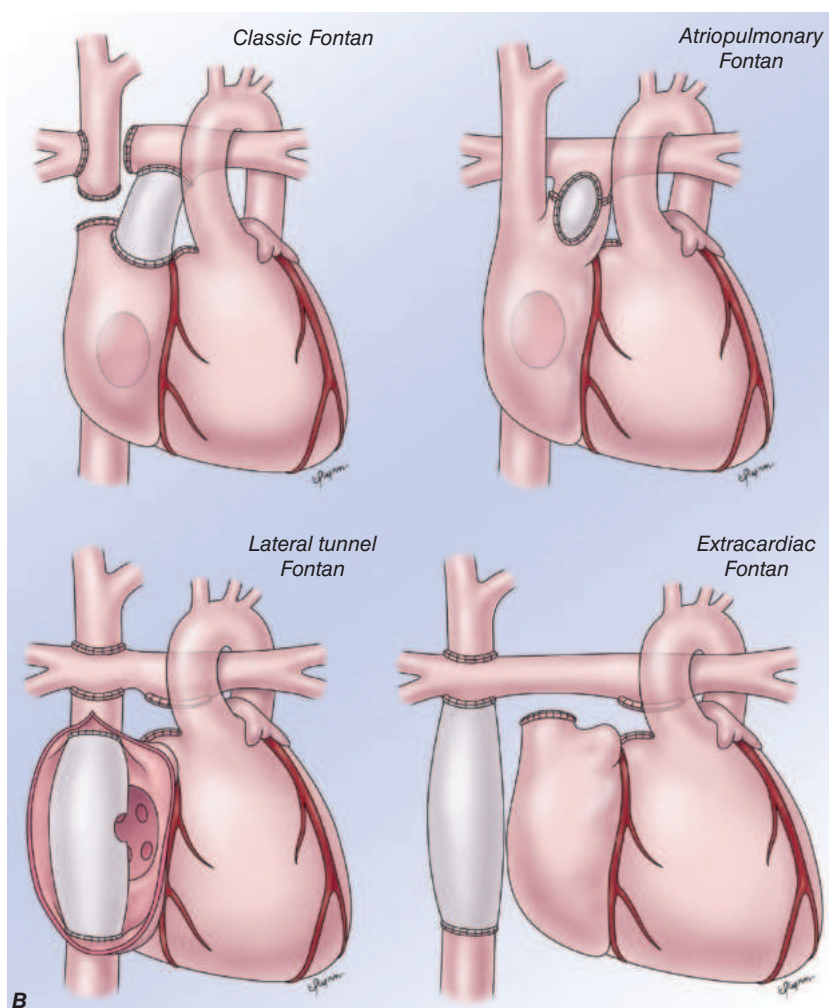
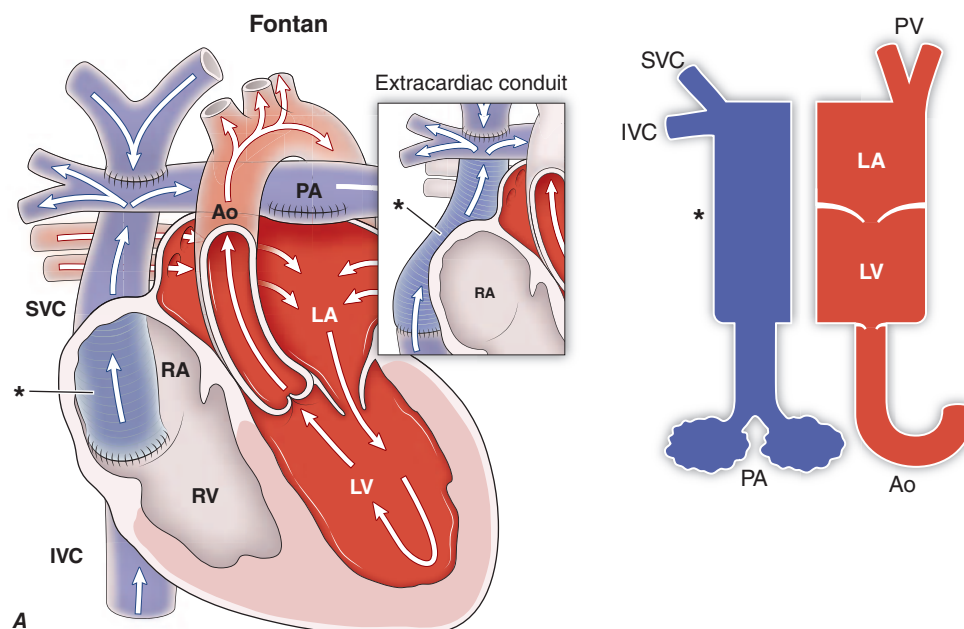


FIGURE 280-12 A. Fontan surgery creates a unique circulation in which deoxygenated blood is directed to the PAs from the SVC and IVC in a fashion that bypasses any pumping chamber. The SVC and IVC are connected (*) via either an internal “tunnel” or an extracardiac conduit that guides flow to the PA. Pulmonary venous (oxygenated) return courses from PV to LA to LV to aorta. In contrast to physiology in normal adults (where pressure is generated by an RV to propel blood flow from a lower pressure RA to a higher pressure LA), in Fontan circulation, by definition, due to the absence of a pumping chamber to the PA, RA pressure is greater than LA pressure, permitting flow through the lungs. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; SVC, superior vena cava; *, Fontan baffle. **B.** Diagrammatic representation of the location of various types of Fontan operations. (Part B used with permission from Emily Flynn McIntosh, illustrator.)

Eisenmenger Syndrome ES is felt to be the consequence of a long-standing high-volume or pressurized left-to-right shunt in which excessive blood flow to the pulmonary vasculature leads to severely increased pulmonary vascular resistance that eventually results in reversal of the shunt, creating bidirectional or right-to-left flow. ES is a multiple-organ condition and may occur with any CHD with an initial left-to-right shunt. The natural history of ES is variable, and although there is significant morbidity, in general, adults with ES appear to survive longer than those with other forms of pulmonary arterial hypertension. Medical care recommendations have included sustaining adequate hydration, avoiding, and treating anemia including iron supplementation when appropriate, and anticoagulation (although this remains controversial due to predisposition to bleeding and occurrence of clinical hemoptysis, which has frequently been associated with pulmonary vascular thrombosis). Elevation of hematocrit above that considered appropriate for the degree of cyanosis can be managed in symptomatic patients by hydration alone or, on occasion, by performing phlebotomy with isovolumic replenishment. Routine phlebotomy in the asymptomatic adult with ES is contraindicated. Appropriate optimization of iron stores has been demonstrated to improve quality of life and functional performance in iron-deficient adults with ES. Contraception for women with ES who are of childbearing age is strongly recommended, avoiding use of estrogen, which may be thrombogenic. Pregnancy is contraindicated in these women due to the high risk of maternal mortality.

Selective pulmonary vasodilators, such as bosentan or sildenafil, are efficacious in ES. Select patients may be candidates for combined heart-lung transplantation or preferably lung transplantation with concomitant repair of the intracardiac defect, if feasible.

The Role of Palliative Care in ACHD In aggregate, adults with CHD demonstrate both quality-of-life-limiting comorbidities and premature mortality far in excess of age-matched controls. The reported prevalence of pain, anxiety, depression, dyspnea, and fatigue appears similar to that reported for adults who are decades older and engaged in palliative care for acquired cardiovascular disease at end of life (EOL). Similarly, at EOL with ACHD, frequencies of hospitalization, intensive care admission, 30-day readmission, and increased length of hospital stay appear greater (despite younger age) than for adults with cancer. In a retrospective study of ACHD patients who died during a hospital admission, only a minority had engaged in EOL discussions with their providers. Surveys of both adults with CHD and their providers suggest that the overwhelming majority of patients wish to participate in advanced care planning and discussion of palliative care; this contrasts with statements from ACHD care providers noting their uncertainties regarding EOL prognostication and concerns over discussion about EOL. Palliative care specialists who are embedded within or aligned with ACHD care teams can play an important and iterative role in defining and addressing alignment of patient and clinician goals within the boundaries of frequently complex care decisions over the adult life span.

Global Considerations As survival patterns improve for all medically complex patients, the internist and general practitioner are faced with particular challenges and dilemmas; foremost is accrual of sufficient knowledge and competency so as to be able both to engage in patient care provision as well as to seek greater expertise, guidance, and support, when such is appropriate. Across the globe, lifelong care for adults with CHD typifies this growing demand. Care for adults with CHD within medical care centers that contain an ACHD specialty care program has been associated with improved overall survival. However, current analyses suggest that the majority of adults with CHD seek and receive their medical care outside of such ACHD specialty care centers and within the hands of the general practitioner, internist, and cardiologist. Under a surface of adaptability and determination, adults with CHD present a wide spectrum of cognitive and functional performance, multiple organ system comorbidities, abnormalities of systemic and pulmonary vasculature, and a near universal presence of heart

failure of one stage or another, all over a lifetime. It appears incumbent on the ACHD specialist and ACHD specialty care centers to serve as a hub for partnering practitioners, encouraging engagement to the level of highest competencies, and providing education, oversight, and support, so as to achieve optimal outcomes.

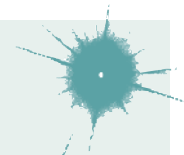
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281

Pericardial Disease

Joseph Loscalzo



■ NORMAL FUNCTIONS OF THE PERICARDIUM

The normal pericardium is a double-layered sac of the visceral pericardium and parietal pericardium. The visceral pericardium is a serous membrane that is separated from the fibrous parietal pericardium by a small quantity (15–50 mL) of fluid, an ultrafiltrate of plasma. The normal pericardium, by exerting a restraining force, prevents sudden dilation of the cardiac chambers, especially the right atrium and ventricle, e.g., during exercise. It also restricts the anatomic position of the heart and likely retards the spread of infections from the lungs and pleural cavities to the heart. Nevertheless, *total* absence of the pericardium, either congenital or after surgery, does not produce obvious clinical disease. In *partial* left pericardial defects, the main pulmonary artery and left atrium may bulge through the defect; very rarely, herniation and subsequent strangulation of the left atrium may cause sudden death.

ACUTE PERICARDITIS

Acute pericarditis, by far the most common pathologic process involving the pericardium (Table 281-1), has four principal diagnostic features:

1. *Chest pain* is usually present in acute infectious pericarditis and in many of the forms presumed to be related to hypersensitivity,

TABLE 281-1 Classification of Pericarditis

Clinical Classification

- I. Acute pericarditis (<6 weeks)
 - A. Fibrinous
 - B. Effusive (serous or sanguineous)
- II. Subacute pericarditis (6 weeks to 6 months)
 - A. Effusive-constrictive
 - B. Constrictive
- III. Chronic pericarditis (>6 months)
 - A. Constrictive
 - B. Adhesive (nonconstrictive)

Etiologic Classification

- I. Infectious pericarditis
 - A. Viral (coxsackievirus A and B, echovirus, herpesviruses, mumps, adenovirus, hepatitis, HIV, post-acute COVID, mpox)
 - B. Pyogenic (pneumococcus, *Streptococcus*, *Staphylococcus*, *Neisseria*, *Legionella*, *Chlamydia*)
 - C. Tuberculous
 - D. Fungal (histoplasmosis, coccidioidomycosis, *Candida*, blastomycosis)
 - E. Other infections (syphilitic, protozoal, parasitic)
- II. Noninfectious pericarditis
 - A. Acute idiopathic
 - B. Renal failure
 - C. Neoplasia
 1. Primary tumors (benign or malignant, mesothelioma)
 2. Tumors metastatic to pericardium (lung and breast cancer, lymphoma, leukemia)
 - D. Trauma (penetrating chest wall, nonpenetrating)
 - E. Aortic dissection (with leakage into pericardial sac)
 - F. Acute myocardial infarction
 - G. Postirradiation
 - H. Familial Mediterranean fever and other autoinflammatory syndromes
 - I. Familial pericarditis
 1. Mulibrey nanism^a
 - J. Metabolic (myxedema, cholesterol)
- III. Pericarditis presumably related to autoimmunity
 - A. Rheumatic fever
 - B. Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, acute rheumatic fever, granulomatosis with polyangiitis, IgG4 disease)
 - C. Drug-induced (e.g., procainamide, hydralazine, phenytoin, isoniazid, minoxidil, anticoagulants, methysergide)
 - D. Postcardiac injury
 1. Postpericardiotomy
 2. Posttraumatic
 3. Postmyocardial infarction (Dressler's syndrome)

^aAn autosomal recessive syndrome characterized by growth failure, muscle hypotonia, hepatomegaly, ocular changes, enlarged cerebral ventricles, intellectual disability, ventricular hypertrophy, and chronic constrictive pericarditis.

Abbreviation: COVID, coronavirus disease.

autoimmunity, or of unknown cause (idiopathic). The pain of acute pericarditis is often severe, retrosternal and/or left precordial, and referred to the neck, arms, or left shoulder. Frequently the pain is pleuritic, consequent to accompanying pleural inflammation (i.e., sharp and aggravated by inspiration and coughing); however, at times, it is steady, radiates to the trapezius ridge or into either arm, and resembles that of myocardial ischemia. For this reason, confusion with acute myocardial infarction (AMI) is common. Characteristically, pericardial pain may be intensified by lying supine and relieved by sitting up and leaning forward (Chap. 15). Pain is often absent in slowly developing tuberculous, postirradiation, neoplastic, and uremic pericarditis.

The differentiation of AMI from acute pericarditis may be challenging when, with the latter, serum biomarkers of myocardial damage rise, presumably because of concomitant involvement of the

epicardium in the inflammatory process (an epi-myocarditis) with resulting myocyte necrosis. If they occur, however, these elevations are quite modest compared to those in AMI, given the superficial (sub-)epicardial injury despite often extensive electrocardiographic ST-segment elevation in pericarditis. This dissociation is useful in differentiating between these conditions.

2. A *pericardial friction rub* is audible at some point in the illness in approximately 85% of patients with acute pericarditis. The rub may have up to three components per cardiac cycle and is described as rasping, scratching, or grating (Chap. 246); it is heard most frequently at end expiration with the patient upright and leaning forward.
3. The *electrocardiogram* (ECG) in acute pericarditis without massive effusion usually displays changes secondary to acute subepicardial inflammation (Fig. 281-1A), and typically evolves through four stages. In stage 1, there is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V_1 – V_6 , with reciprocal depressions only in aVR and occasionally V_1 . In addition, there is depression of the PR segment below the TP segment, reflecting atrial involvement, an early change that may occur prior to ST segment elevation. Usually there are no significant changes in QRS complexes unless a large pericardial effusion develops (see below). After several days, the ST segments return to normal (stage 2), and only then, or even later, do the T waves become inverted (stage 3). Weeks or months after the onset of acute pericarditis, the ECG returns to normal (stage 4). In contrast, in AMI, ST elevations are upwardly convex, and reciprocal depression is usually more prominent; these changes may return to normal within a day or two (Chaps. 285 and 286).
4. *Pericardial effusion* is usually associated with pain and/or the ECG changes mentioned above and, if the effusion is large, with electrical alternans (Fig. 281-1B). Pericardial effusion is especially important clinically when it develops within a relatively short time because it may lead to cardiac tamponade (see below). Differentiation from cardiac enlargement on physical examination may be difficult, but heart sounds may be fainter with large pericardial effusion. The friction rub and the apex impulse may disappear. The base of the left lung may be compressed by pericardial fluid, producing *Ewart's sign*, a patch of dullness, increased fremitus, and egophony beneath the angle of the left scapula. The chest x-ray may show enlargement of the cardiac silhouette, with a “water bottle” configuration, but may be normal in patients with small effusions.

Diagnosis *Echocardiography* (Chap. 248) is the most widely used imaging technique. It is sensitive, specific, simple, and noninvasive; may be performed at the bedside; and allows localization and estimation of the quantity of pericardial fluid. The presence of pericardial fluid is recorded by two-dimensional transthoracic echocardiography as a relatively echo-free space between the posterior pericardium and left ventricular epicardium and/or as a space between the anterior right ventricle and the parietal pericardium just beneath the anterior chest wall (Fig. 281-2).

The diagnosis of pericardial fluid or thickening may be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). These techniques may be superior to echocardiography in detecting loculated pericardial effusions and pericardial thickening, and in the identification of pericardial masses. MRI is also helpful in detecting pericardial inflammation (Fig. 281-3).

TREATMENT

Acute Pericarditis

There is no specific therapy for acute idiopathic pericarditis, but bed rest may be recommended, and anti-inflammatory treatment with aspirin (2–4 g/d) or nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (600–800 mg tid) or indomethacin (25–50 mg tid), should be administered along with gastric protection (e.g., omeprazole 20 mg/d). In responsive

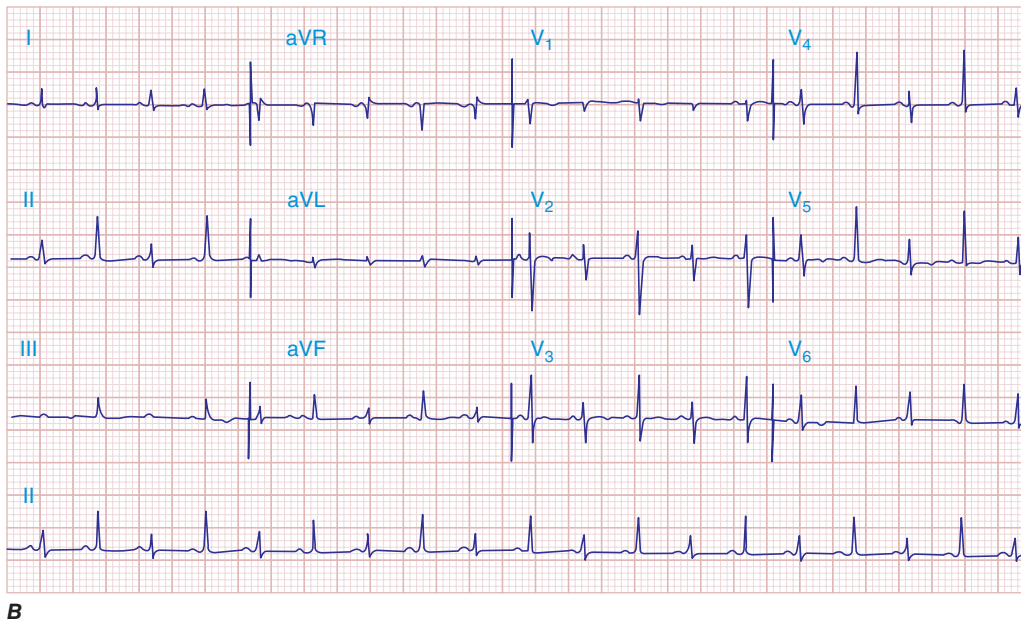
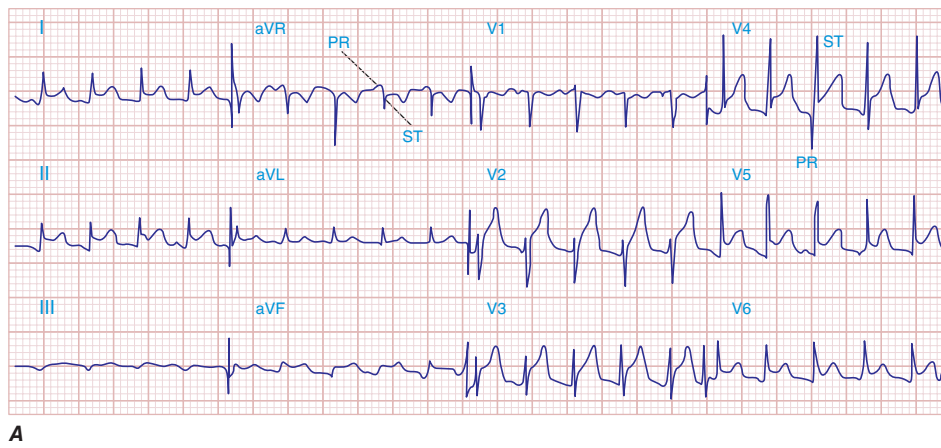


FIGURE 281-1 A. Acute pericarditis. There are diffuse ST-segment elevations in leads I, II, aVF, and V₂–V₆. There is PR-segment depression due to a concomitant atrial injury current. **B.** Electrical alternans. This tracing was obtained from a patient with a large pericardial effusion with cardiac tamponade.

patients, these doses should be continued for 1–2 weeks and then tapered over several weeks. In addition, colchicine (0.5 to 0.6 mg qd [<70 kg] or 0.5 to 0.6 mg bid [>70 kg]) should be administered for 3 months. Colchicine enhances the response to NSAIDs

and also aids in reducing the risk of recurrent pericarditis. This drug is concentrated in and interferes with the migration of neutrophils, may cause diarrhea and other gastrointestinal side effects, and is contraindicated in patients with hepatic or renal dysfunction. Glucocorticoids (e.g., prednisone 1 mg/kg per day) usually suppress the clinical manifestations of acute pericarditis in patients who have failed therapy with or do not tolerate NSAIDs and colchicine. However, since they increase the risk of subsequent recurrence, full-dose corticosteroids should be given for only 2–4 days and then tapered. Anticoagulants should be avoided because their use could cause bleeding into the pericardial cavity and tamponade.

In patients with multiple, frequent, and disabling recurrences that continue for >2 years, are not prevented by continuing colchicine and other NSAIDs, and are not controlled by glucocorticoids, treatment with azathioprine or anakinra (an interleukin 1 β receptor antagonist) has been reported to be of benefit. Rarely, pericardial stripping may be necessary; however, this procedure may not always terminate the recurrences.

The majority of patients with acute pericarditis can be managed as outpatients with careful follow-up. However, when specific causes (tuberculosis, neoplastic disease, bacterial infection) are suspected, or if any of the predictors of poor prognosis (fever $>38^{\circ}\text{C}$, subacute onset, large pericardial effusion, immunosuppression, or evidence of pericardial tamponade) are present, hospitalization is advisable.

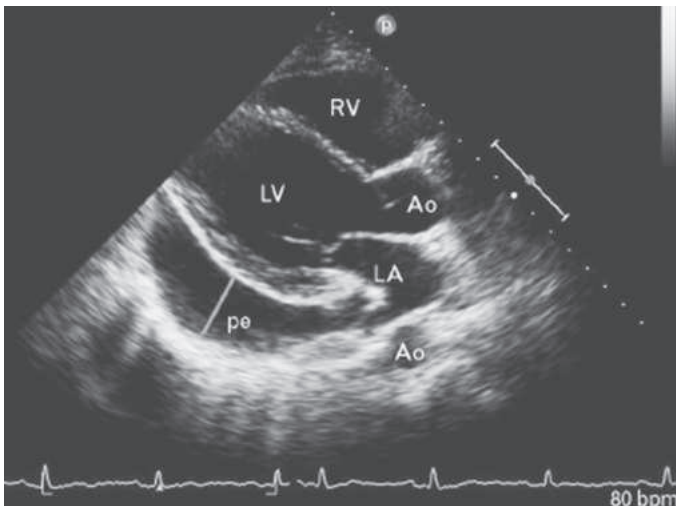


FIGURE 281-2 Two-dimensional echocardiogram in lateral view in a patient with a large pericardial effusion. Ao, aorta; LA, left atrium; LV, left ventricle; pe, pericardial effusion; RV, right ventricle. (Reproduced with permission from Imazio M: Contemporary management of pericardial diseases. *Curr Opin Cardiol* 27:308, 2012.)

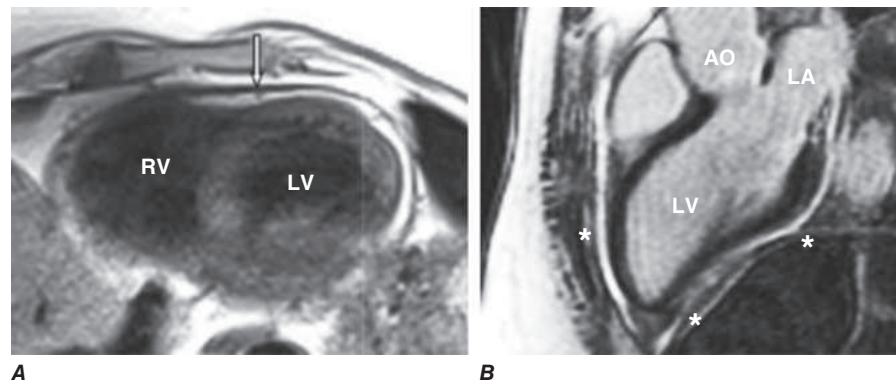


FIGURE 281-3 Pericardial inflammation by cardiac magnetic resonance imaging. A. Short axis view. The pericardium is thickened and enhanced on T2 magnetic images. Note thickened white line denoted by arrow. **B.** Long axis view. Late gadolinium enhancement of thickened, inflamed pericardium. AO, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (From RY Kwong: *Cardiovascular magnetic resonance imaging*, in Braunwald's *Heart Disease*, 10th ed, Mann DL et al [eds]. Philadelphia: Elsevier, 2015, pp 320–40.)

CARDIAC TAMPONADE

The accumulation of fluid in the pericardial space in a quantity sufficient to cause serious obstruction of the inflow of blood into the ventricles results in cardiac tamponade. This complication may be fatal if it is not recognized and treated promptly. The most common causes of tamponade are idiopathic pericarditis and pericarditis secondary to neoplastic disease, tuberculosis, or bleeding into the pericardial space after leakage from an aortic dissection, cardiac operation, trauma, or treatment with anticoagulants.

The three principal features of tamponade (*Beck's triad*) are hypotension, soft or absent heart sounds, and jugular venous distention with a prominent *x* (early systolic) descent but an absent *y* (early diastolic) descent. The limitations to ventricular filling are responsible for reductions of cardiac output and arterial pressure. The quantity of fluid necessary to produce cardiac tamponade may be as small as 200 mL when the fluid develops rapidly or be as much as >2000 mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume.

A high index of suspicion for cardiac tamponade is required because in many instances no obvious cause for pericardial disease is apparent. This diagnosis should be considered in any patient with otherwise unexplained sudden enlargement of the cardiac silhouette, hypotension, and elevation of jugular venous pressure. Reductions in amplitude of the QRS complexes and *electrical alternans* of the P, QRS, or T waves should also raise the suspicion of cardiac tamponade (Fig. 281-1).

Table 281-2 lists the features that distinguish acute cardiac tamponade from constrictive pericarditis.

Paradoxical Pulse This important clue to the presence of cardiac tamponade consists of a greater than normal (10 mmHg) inspiratory decline in systolic arterial pressure. When severe, it may be detected by palpating weakness or even disappearance of the arterial pulse during inspiration, but usually sphygmomanometric measurement of systolic pressure during slow respiration is required.

Because both ventricles share a tight incompressible covering, i.e., the pericardial sac, the inspiratory enlargement of the right ventricle

TABLE 281-2 Features That Distinguish Cardiac Tamponade from Constrictive Pericarditis and Similar Clinical Disorders

CHARACTERISTIC	TAMPONADE	CONSTRICTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY	RIGHT VENTRICULAR MYOCARDIAL INFARCTION	EFFUSIVE CONSTRICTIVE PERICARDITIS
Clinical					
Pulsus paradoxus	+++	+	+	+	+++
Jugular veins					
Prominent <i>y</i> descent	–	++	+	+	–
Prominent <i>x</i> descent	+++	++	+++	+	+++
Kussmaul's sign	–	+++	+	+++	++
Third heart sound	–	–	+	+	+
Pericardial knock	–	++	–	–	–
Electrocardiogram					
Low ECG voltage	++	++	+	–	+
Electrical alternans	++	–	–	–	+
Echocardiogram					
Thickened pericardium	–	+++	–	–	++
Pericardial calcification	–	++	–	–	–
Pericardial effusion	+++	–	–	–	++
RV size	Usually small	Usually normal	Usually normal	Enlarged	Usually normal
Exaggerated respiratory variation in flow velocity	+++	+++	–	+++	+
CT/MRI					
Thickened pericardium	–	+++	–		++
Equalization of diastolic pressures	+++	+++	–	++	++

Abbreviations: +++, always present; ++, usually present; +, rare; –, absent; CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; RV, right ventricle.

Source: Reproduced with permission from GM Brockington et al: Constrictive pericarditis. *Cardiol Clin* 8:645, 1990.

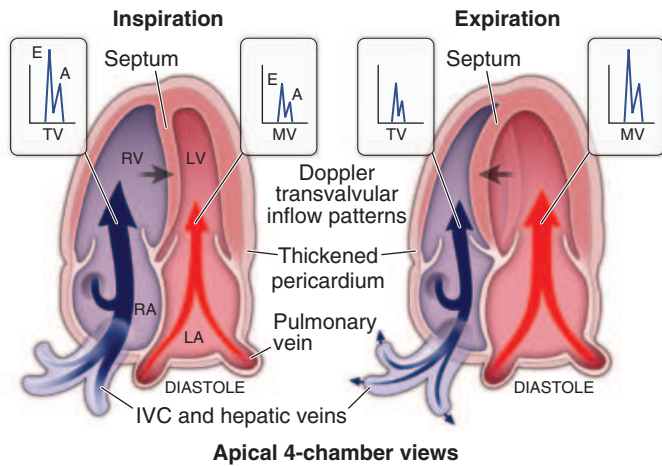


FIGURE 281-4 Constrictive pericarditis. Doppler schema of respirophasic changes in mitral and tricuspid inflow. Reciprocal patterns of ventricular filling are assessed on pulsed Doppler examination of mitral valve (MV) and tricuspid valve (TV) inflow. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Courtesy of Bernard E. Bulwer, MD.)

causes leftward bulging of the interventricular septum, reducing left ventricular volume, stroke volume, and arterial systolic pressure. Paradoxical pulse also occurs in approximately one-third of patients with constrictive pericarditis (see below), and in some cases of hypovolemic shock, acute and chronic obstructive airway disease, and pulmonary embolism. Right ventricular infarction ([Chap. 286](#)) may resemble cardiac tamponade with hypotension, elevated jugular venous pressure, a slow y descent in the jugular venous pulse, and, occasionally, a paradoxical pulse (Table 281-2).

Diagnosis Because immediate treatment of cardiac tamponade may be lifesaving, prompt establishment of the diagnosis, usually by echocardiography, should be undertaken. When pericardial effusion causes tamponade, Doppler ultrasound shows that tricuspid and pulmonic valve flow velocities increase markedly during inspiration, whereas pulmonic vein, mitral, and aortic flow velocities decrease (as in constrictive pericarditis, see below) ([Fig. 281-4](#)). In tamponade, there is late diastolic inward motion (collapse) of the right ventricular free wall and the right atrium. Transesophageal echocardiography, CT, or cardiac MRI may be necessary to diagnose a loculated effusion responsible for cardiac tamponade.

TREATMENT

Cardiac Tamponade

Patients with acute pericarditis should be observed frequently for the development of an effusion. If a large effusion is present, pericardiocentesis should be performed or the patient watched closely for signs of tamponade with serial echocardiography and monitoring of arterial and venous pressures.

PERICARDIOCENTESIS

If manifestations of tamponade appear, pericardiocentesis using an apical, parasternal, or, most commonly, subxiphoid approach must be carried out at once because if left untreated, tamponade may be rapidly fatal. Whenever possible, this procedure should be carried out under echocardiographic guidance. Intravenous saline may be administered as the patient is being readied for the procedure, but the pericardiocentesis must not be delayed. If possible, intrapericardial pressure should be measured before fluid is withdrawn, and the pericardial cavity should be drained as completely as possible. A small, multiholed catheter may be advanced over the needle inserted into the pericardial cavity and left in place to allow draining of the pericardial space if fluid reaccumulates. Surgical drainage through a limited (subxiphoid) thoracotomy may be required in recurrent tamponade to remove loculated effusions and/or when it is necessary to obtain tissue for diagnosis.

Pericardial fluid obtained from an effusion may have the physical characteristics of an exudate. In developed nations, bloody fluid is most commonly due to neoplasm, renal failure, or cardiac trauma. In developing nations, tuberculosis may also cause exudative and/or bloody effusion.

The pericardial fluid should be analyzed for red and white blood cells and cytology for neoplastic cells. Cultures should be obtained. The presence of DNA of *Mycobacterium tuberculosis* determined by the polymerase chain reaction and/or of an elevated adenosine deaminase strongly supports the diagnosis of tuberculous pericarditis; however, it is often necessary to obtain pericardial tissue to make this diagnosis ([Chap. 183](#)).

■ VIRAL OR IDIOPATHIC ACUTE PERICARDITIS

In many instances, acute pericarditis occurs in association with or following illnesses of known or presumed viral origin and probably is caused by the same agent. There may be an antecedent infection of the respiratory tract, but viral isolation and serologic studies are usually negative. In some cases, coxsackievirus A or B or the virus of influenza, echovirus, mumps, herpes simplex, varicella-zoster, adenovirus, or cytomegalovirus has been isolated from pericardial fluid, and/or appropriate elevations in viral antibody titers have been observed. Frequently, a viral cause cannot be established, and the term *idiopathic acute pericarditis* is appropriate.

Viral or idiopathic acute pericarditis occurs at all ages but is most common in young adult males and is often associated with pleural effusion and pneumonitis. The almost simultaneous development of fever and precordial pain, often 10–12 days after a presumed viral illness, constitutes an important feature in the differentiation of acute pericarditis from AMI, in which chest pain precedes fever. The constitutional symptoms are usually mild to moderate, and a pericardial friction rub is often audible. The disease ordinarily runs its course in a few days to 4 weeks. Elevations of C-reactive protein and of the white blood cell count are common. The ST-segment alterations in the ECG usually disappear after 1 or more weeks, but the abnormal T waves may persist for as long as several years and be a source of confusion in persons without a clear history of pericarditis. Accumulation of some pericardial fluid is common, and both tamponade and constrictive pericarditis are possible, but infrequent, complications.

The most frequent complication is recurrent (relapsing) pericarditis, which occurs in approximately one-fourth of patients with acute idiopathic pericarditis. A smaller number of individuals have multiple recurrences.

Postcardiac Injury Syndrome Acute pericarditis may appear in a variety of circumstances that have one common feature—previous injury to the myocardium with blood in the pericardial cavity. The syndrome may develop after a cardiac operation (postpericardiotomy syndrome), after blunt or penetrating cardiac trauma ([Chap. 283](#)), or after perforation of the heart with a catheter; rarely, it follows AMI.

The clinical picture mimics acute viral or idiopathic pericarditis. The principal symptom is the pain of acute pericarditis, which usually develops 1–4 weeks after the cardiac injury. Recurrences are common and may occur up to 2 years or more following the injury. Fever, pleuritis, and pneumonitis are accompanying features, and the illness usually subsides in 1 or 2 weeks. The pericarditis may be of the fibrinous variety, or it may be a pericardial effusion, which is often serosanguinous and rarely causes tamponade. ECG changes typical of acute pericarditis may also occur. This syndrome is probably the result of a hypersensitivity (or autoimmune) reaction to antigen(s) that originate from injured myocardial tissue and/or pericardium.

Often no treatment is necessary aside from aspirin and analgesics. When the illness is severe or followed by a series of disabling recurrences, therapy with another NSAID, colchicine, or a glucocorticoid, such as described for treatment of acute pericarditis, is usually effective.

■ DIFFERENTIAL DIAGNOSIS

Because there is no specific test for *acute idiopathic pericarditis*, the diagnosis is one of exclusion. Consequently, all other disorders that

may be associated with acute fibrinous pericarditis must be considered. A common diagnostic error is mistaking acute viral or idiopathic pericarditis for AMI and vice versa.

Pericarditis secondary to postcardiac injury is differentiated from acute idiopathic pericarditis chiefly by timing. If it occurs within a few days or weeks of a chest blow, a cardiac perforation, a cardiac operation, or an AMI, the two are probably related.

It is important to distinguish *pericarditis due to collagen vascular disease* from acute idiopathic pericarditis. Most important in the differential diagnosis is the pericarditis due to systemic lupus erythematosus (SLE; **Chap. 368**) or drug-induced (hydralazine or procainamide) lupus. When pericarditis occurs in the absence of any obvious underlying disorder, the diagnosis of SLE may be suggested by a rise in the titer of antinuclear antibodies. Acute pericarditis is an occasional complication of *rheumatoid arthritis*, *scleroderma*, and *polyarteritis nodosa*, and other evidence of these diseases is usually obvious at the time of presentation with acute pericarditis.

Pyogenic (purulent) pericarditis is usually secondary to cardiothoracic operations, by extension of infection from the lungs or pleural cavities, from rupture of the esophagus into the pericardial sac, or from rupture of a valvular ring abscess in a patient with infective endocarditis. It may also complicate the viral, bacterial, mycobacterial, and fungal infections that occur with HIV infection. It is generally accompanied by fever, chills, septicemia, and evidence of infection elsewhere, and generally has a poor prognosis. The diagnosis is made by examination of the pericardial fluid. It requires immediate drainage as well as vigorous antibiotic treatment.

Pericarditis of renal failure (uremic pericarditis) occurs in up to one-third of patients with severe renal dysfunction and is also seen in patients undergoing chronic dialysis who have normal levels of blood urea nitrogen (*dialysis-associated pericarditis*). These two forms of pericarditis may be fibrinous and are generally associated with serosanguinous effusions; frank hemorrhagic effusions may be seen in some cases of uremic pericarditis prior to the onset of dialysis. A pericardial friction rub is common, but pain is usually absent or mild. Treatment with an NSAID and intensification of dialysis are usually adequate. Occasionally, tamponade occurs and pericardiocentesis is required. When the pericarditis of renal failure is recurrent or persistent, a pericardial window should be created or pericardiectomy may be necessary.

Pericarditis due to *neoplastic diseases* results from extension or invasion of metastatic tumors (most commonly carcinoma of the lung and breast, malignant melanoma, lymphoma, and leukemia) to the pericardium. The pain of pericarditis, tamponade, and atrial arrhythmias are complications that occur occasionally. Diagnosis is made by pericardial fluid cytology or pericardial biopsy. *Mediastinal irradiation* for neoplasm may cause acute pericarditis and/or chronic constrictive pericarditis. Unusual causes of acute pericarditis include syphilis, fungal infection (histoplasmosis, blastomycosis, aspergillosis, and candidiasis), and parasitic infestation (amebiasis, toxoplasmosis, echinococcosis, and trichinosis) (Table 281-1).

■ CHRONIC PERICARDIAL EFFUSIONS

Chronic pericardial effusions are sometimes encountered in patients without an antecedent history of acute pericarditis. They may cause few symptoms per se, and their presence may be detected by finding an enlarged cardiac silhouette on a chest roentgenogram. *Tuberculosis* and *myxedema* may be causal. Neoplasms, SLE, rheumatoid arthritis, mycotic infections, radiation therapy to the chest, and chylopericardium may also cause chronic pericardial effusion and should be considered and specifically sought in such patients. Aspiration and analysis of the pericardial fluid are often helpful in diagnosis. Pericardial fluid should be analyzed as described under pericardiocentesis. Grossly sanguineous pericardial fluid results most commonly from a neoplasm, tuberculosis, renal failure, or slow leakage from an aortic dissection. Pericardiocentesis may resolve large effusions, but pericardiectomy may be required in patients with recurrence. Intrapericardial instillation of sclerosing agents may be used to prevent reaccumulation of fluid, most commonly in recurrent neoplastic effusions.

CHRONIC CONSTRICTIVE PERICARDITIS

This disorder results when the healing of an acute fibrinous or serofibrinous pericarditis or the resorption of a chronic pericardial effusion is followed by obliteration of the pericardial cavity with the formation of granulation tissue. The latter gradually contracts and forms a firm scar encasing the heart, which may become calcified. In developing nations, a high percentage of cases are of tuberculous origin, but this is now an uncommon cause in North America or Western Europe. Chronic constrictive pericarditis may follow acute or relapsing viral or idiopathic pericarditis, trauma with organized blood clot, or cardiac surgery of any type, or results from mediastinal irradiation, purulent infection, histoplasmosis, neoplastic disease (especially breast cancer, lung cancer, and lymphoma), rheumatoid arthritis, SLE, or chronic renal failure treated by chronic dialysis. In many patients, the cause of the pericardial disease is undetermined, and in these patients, an asymptomatic or forgotten bout of viral pericarditis, idiopathic or acute, may have been the inciting event.

The basic physiologic abnormality in patients with chronic constrictive pericarditis is the inability of the ventricles to fill owing to the limitations imposed by the rigid, thickened pericardium. Ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, whereas in cardiac tamponade, ventricular filling is impeded throughout diastole. In both conditions, ventricular end-diastolic and stroke volumes are reduced and the end-diastolic pressures in both ventricles and the mean pressures in the atria, pulmonary veins, and systemic veins are all elevated to similar levels (i.e., within 5 mmHg of one another). Despite these hemodynamic changes, systolic function may be normal or only slightly impaired at rest. However, in advanced cases, the fibrotic process may extend into the myocardium and cause myocardial scarring and atrophy, and venous congestion may then be due to the combined effects of the pericardial and myocardial lesions.

In constrictive pericarditis, the right and left atrial pressure pulses display an M-shaped contour, with prominent *x* and *y* descents. The *y* descent, which is absent or diminished in cardiac tamponade, is the most prominent deflection in constrictive pericarditis; it reflects rapid early filling of the ventricles. The *y* descent is interrupted by a rapid rise in atrial pressure during early diastole, when ventricular filling is impeded by the constricting pericardium. These characteristic changes are transmitted to the jugular veins where they may be recognized by inspection. In constrictive pericarditis, the ventricular pressure pulses in both ventricles exhibit the characteristic “square root” sign during diastole. These hemodynamic changes, although characteristic, are not pathognomonic of constrictive pericarditis and may also be observed in restrictive cardiomyopathies (**Chaps. 266–270, Table 266-1**).

■ CLINICAL AND LABORATORY FINDINGS

Weakness, fatigue, weight gain, increased abdominal girth, abdominal discomfort, and edema are common. The patient often appears chronically ill, and in advanced cases, anasarca, skeletal muscle wasting, and cachexia may be present. Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe. The neck veins are distended and may remain so even after intensive diuretic treatment, and venous pressure may fail to decline during inspiration (*Kussmaul's sign*). The latter is common in chronic pericarditis but may also occur in tricuspid stenosis, right ventricular infarction, and restrictive cardiomyopathy.

The pulse pressure is normal or reduced. A paradoxical pulse can be detected in about one-third of cases. Congestive hepatomegaly is pronounced, may impair hepatic function, and may cause jaundice; ascites is common and is usually more prominent than dependent edema. Pleural effusions and splenomegaly may also be present. The apical pulse is reduced and may retract in systole (*Broadbent's sign*). The heart sounds may be distant; an early third heart sound (i.e., a pericardial knock) occurring at the cardiac apex with the abrupt cessation of ventricular filling is often conspicuous.

The ECG frequently displays low voltage of the QRS complexes and diffuse flattening or inversion of the T waves. Atrial fibrillation is present in about one-third of patients. The *chest roentgenogram* shows

a normal or slightly enlarged heart. Pericardial calcification is most common in tuberculous pericarditis. Pericardial calcification may, however, occur in the absence of constriction, and constriction may occur without calcification.

Inasmuch as the common physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or absent in chronic constrictive pericarditis, hepatic enlargement and dysfunction associated with jaundice and intractable ascites may lead to a mistaken diagnosis of hepatic cirrhosis. This error can be avoided if the neck veins are inspected and found to be distended with the characteristic waveform features.

The transthoracic *echocardiogram* often shows pericardial thickening, dilation of the inferior vena cava and hepatic veins, and a sharp halt to rapid left ventricular filling in early diastole, with normal ventricular systolic function and flattening of the left ventricular posterior wall. There is a distinctive pattern of transvalvular flow velocity on Doppler echocardiography (Fig. 281-4). During inspiration, there is an exaggerated reduction in blood flow velocity in the pulmonary veins and across the mitral valve, and a leftward shift of the ventricular septum; the opposite occurs during expiration. Diastolic flow velocity in the inferior vena cava into the right atrium and across the tricuspid valve increases in an exaggerated manner during inspiration and declines during expiration. However, echocardiography cannot definitively establish or exclude the diagnosis of constrictive pericarditis; CT and MRI are more accurate, with the latter useful in evaluating myocardial involvement.

■ DIFFERENTIAL DIAGNOSIS

As with chronic constrictive pericarditis, cor pulmonale (Chap. 264) may be associated with marked systemic venous hypertension, little pulmonary congestion, a (left) heart that is not enlarged, and a paradoxical pulse. However, in cor pulmonale, advanced parenchymal pulmonary disease is usually apparent and venous pressure *falls* during inspiration (i.e., Kussmaul's sign is negative). *Tricuspid stenosis* (Chap. 277) may also simulate chronic constrictive pericarditis with congestive hepatomegaly, splenomegaly, ascites, and venous distention. However, the characteristic murmur and that of accompanying mitral stenosis are usually present.

Because it can be corrected surgically, it is important to distinguish chronic constrictive pericarditis from restrictive cardiomyopathy (Chap. 266), which has a similar pathophysiologic underpinning (i.e., restriction of ventricular filling). The differentiating features are summarized in Table 281-2. When a patient has progressive, disabling, and unresponsive congestive heart failure and displays any of the features of constrictive heart disease, Doppler echocardiography to record respiratory effects on transvalvular flow (Fig. 281-4) should be performed and an MRI or CT scan should be obtained to detect or exclude constrictive pericarditis because the latter is usually correctable.

TREATMENT

Constrictive Pericarditis

Pericardial resection is the only definitive treatment of constrictive pericarditis and should be as complete as possible. Coronary arteriography should be carried out preoperatively in patients aged >50 years to exclude accompanying coronary artery disease. The benefits derived from cardiac decortication are usually progressive over a period of months. The risk of this operation depends on the extent of penetration of the myocardium by the fibrotic and calcific process, the severity of myocardial atrophy, the extent of secondary impairment of hepatic and/or renal function, and the patient's general condition. Operative mortality is in the range of 5–10% even in experienced centers; the patients with the most severe disease, especially secondary to radiation therapy, are at highest risk. Therefore, surgical treatment should, if possible, be carried out as early as possible.

Subacute Effusive-Constrictive Pericarditis This form of pericardial disease is characterized by the combination of a tense effusion in the pericardial space and constriction of the heart by thickened

pericardium. As such, it shares a number of features with both chronic pericardial effusion producing cardiac compression and with pericardial constriction. It may be caused by tuberculosis (see below), multiple attacks of acute idiopathic pericarditis, radiation, traumatic pericarditis, renal failure, scleroderma, and neoplasms. The heart is generally enlarged, and a paradoxical pulse is usually present. After pericardiocentesis, the physiologic findings may change from those of cardiac tamponade to those of pericardial constriction. Furthermore, the intrapericardial pressure and the central venous pressure may decline, but not to normal. The diagnosis can be established by pericardiocentesis followed by pericardial biopsy. Wide excision of both the visceral and parietal pericardium is usually effective therapy.

Tuberculous Pericardial Disease This chronic infection is a common cause of chronic pericardial effusion, especially in the developing world where active tuberculosis and HIV are endemic. Tuberculous pericarditis may present as pericardial effusion, chronic constrictive pericarditis, or subacute effusive-constrictive pericarditis (see above). The clinical picture is that of a chronic, systemic illness in a patient with pericardial effusion. It is important to consider this diagnosis in a patient with known tuberculosis, with HIV, and with fever, chest pain, weight loss, and enlargement of the cardiac silhouette of undetermined origin. If the etiology of chronic pericardial effusion remains obscure despite detailed analysis including culture of the pericardial fluid, a pericardial biopsy, preferably by a limited thoracotomy, should be performed. If definitive evidence is still lacking but the specimen shows granulomas with caseation, antituberculous chemotherapy (Chap. 183) is indicated.

If the biopsy specimen shows a thickened pericardium after 2–4 weeks of antituberculous therapy, pericardiectomy should be performed to prevent the development of constriction. Tubercular cardiac constriction should be treated surgically while the patient is receiving antituberculous chemotherapy.

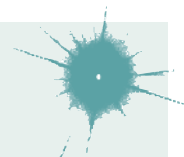
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282

Atrial Myxoma and Other Cardiac Tumors

Stephen Tsaour, Eric H. Awtry



Cardiac tumors can be broadly classified into those that arise primarily in the heart and those that reflect metastatic disease from a distant primary source. Primary cardiac tumors can be further divided into those that are pathologically benign and those that are malignant.

TABLE 282-1 Imaging Modalities and Their Utility in the Evaluation of Cardiac Tumors

MODALITY	UTILITY IN CARDIAC TUMOR EVALUATION
Transthoracic echocardiography (TTE) (including two-dimensional, three-dimensional, and contrast)	Assessment of tumor location and size and its impact on adjacent structures (e.g., valves, pericardium).
Transesophageal echocardiography (TEE)	Improved tumor characterization and spatial resolution compared with TTE. May aid in determining surgical approach.
Cardiac magnetic resonance imaging (MRI) with gadolinium contrast	Improved tissue characterization, definition of tumor size, and identification of local invasion when compared with TTE or TEE. May differentiate tumor from thrombus.
Gated cardiac computed tomography (CT)	Provides anatomic assessment and tissue characterization of the tumor. Useful when patients cannot tolerate MRI or when MRI is not feasible (e.g., patients with implantable cardiac devices). Allows for better assessment of calcified lesions and evaluation of extracardiac tumor involvement.
Nuclear imaging (including ^{18}F -fluorodeoxyglucose positron emission tomography [FDG-PET])	Definition of extracardiac disease. May be useful in diagnosis of certain cardiac tumors (e.g., neuroendocrine tumors), but assessment of smaller tumors may be limited by surrounding myocardial FDG uptake.

Overall, primary cardiac tumors are relatively uncommon, whereas secondary involvement of the heart or pericardium occurs in as many as 20% of patients with end-stage metastatic cancer. While patients with cardiac tumors may present with a variety of symptoms, many patients are asymptomatic at the time of diagnosis, with the tumor being identified incidentally on imaging studies performed for other reasons. Cardiac tumors need to be differentiated from other cardiac masses such as vegetation, thrombus, inflammatory myofibroblastic tumors, or myocardial hypertrophy. Echocardiography is usually the initial imaging modality used to evaluate cardiac tumors; however, a variety of imaging modalities are now available, and a multimodality approach is often necessary for accurate diagnosis and clarification of treatment options (Table 282-1). When diagnosis is uncertain after echocardiography, cardiac magnetic resonance imaging (MRI) is often useful to help further differentiate lesions. Imaging characteristics, including size, location, presence of myocardial infiltration, and first pass perfusion of gadolinium contrast agents, can help differentiate benign from malignant tumors. However, tissue histology remains the gold standard for diagnosis of cardiac tumors.

PRIMARY TUMORS

Primary tumors of the heart are rare, occurring in ~1 in 2000 patients in autopsy series. Approximately three-quarters are histologically benign, the majority of which are myxomas. Malignant tumors, almost all of which are sarcomas, account for 25% of primary cardiac tumors. All cardiac tumors, regardless of pathologic type, have the potential to cause life-threatening complications. Many tumors are now surgically curable; thus, early diagnosis is imperative.

Clinical Presentation Cardiac tumors may present with a wide array of cardiac and noncardiac manifestations. These manifestations, which depend in large part on the location and size of the tumor as well as its impact on surrounding cardiac structures, are often nonspecific features of more common forms of heart disease, and include chest pain, syncope, congestive heart failure (CHF), murmurs, arrhythmias, conduction disturbances, pericardial effusion, and pericardial tamponade. Additionally, embolic phenomena and constitutional symptoms may occur.

Myxoma Myxomas are the most common type of primary cardiac tumor in adults, accounting for one-third to one-half of all cases at postmortem examination, and approximately three-quarters of the tumors treated surgically. They occur at all ages most commonly in the

third through sixth decades, with a female predilection. Approximately 90% of myxomas are sporadic; the remainder are familial with autosomal dominant transmission. The familial variety often occurs as part of a syndrome complex (Carney complex) that includes (1) myxomas (cardiac, skin, and/or breast), (2) lentigines and/or pigmented nevi, and (3) endocrine overactivity (primary nodular adrenal cortical disease with or without Cushing's syndrome, testicular tumors, and/or pituitary adenomas with gigantism or acromegaly). The genetic basis of this complex has not been elucidated completely; however, inactivating mutations in the tumor-suppressor gene *PRKARIA*, which encodes the protein kinase A type I- α regulatory subunit, have been identified in ~70% of patients with Carney complex.

Pathologically, myxomas are gelatinous structures that consist of myxoma cells embedded in a stroma rich in glycosaminoglycans. Most sporadic tumors are solitary, arise from the interatrial septum in the vicinity of the fossa ovalis (particularly in the left atrium), and are often pedunculated on a fibrovascular stalk. In contrast, familial or syndromic tumors tend to occur in younger individuals, are often multiple, may be ventricular in location, and are more likely to recur after initial resection.

Myxomas commonly present with obstructive signs and symptoms. The most common clinical presentation mimics that of mitral valve disease: either stenosis owing to tumor prolapse into the mitral orifice or regurgitation resulting from tumor-induced valvular trauma or distortion. Ventricular myxomas may cause outflow tract obstruction similar to that caused by subaortic or subpulmonic stenosis. The symptoms and signs of myxoma may be sudden in onset or positional in nature, owing to the effects of gravity on tumor position. A characteristic low-pitched sound, a "tumor plop," may be appreciated on auscultation during early or mid-diastole and is thought to result from the impact of the tumor against the mitral valve or ventricular wall. Myxomas also may present with peripheral or pulmonary embolic phenomenon (resulting from embolization of tumor fragments or tumor-associated thrombus) or with constitutional signs and symptoms, including fever, weight loss, cachexia, malaise, arthralgias, rash, digital clubbing, and Raynaud's phenomenon. These constitutional symptoms are likely the result of cytokines (e.g., interleukin 6) secreted by the myxoma. Laboratory abnormalities, such as hypergammaglobulinemia, anemia, polycythemia, leukocytosis, thrombocytopenia or thrombocytosis, elevated erythrocyte sedimentation rate, and elevated C-reactive protein level are often present. These features account for the frequent misdiagnosis of patients with myxomas as having endocarditis, collagen vascular disease, or a paraneoplastic syndrome.

Two-dimensional and three-dimensional transthoracic and/or transesophageal echocardiography are useful in the diagnosis of cardiac myxoma and allow for assessment of tumor size and determination of the site of tumor attachment, both of which are important considerations in the planning of surgical excision (Fig. 282-1).

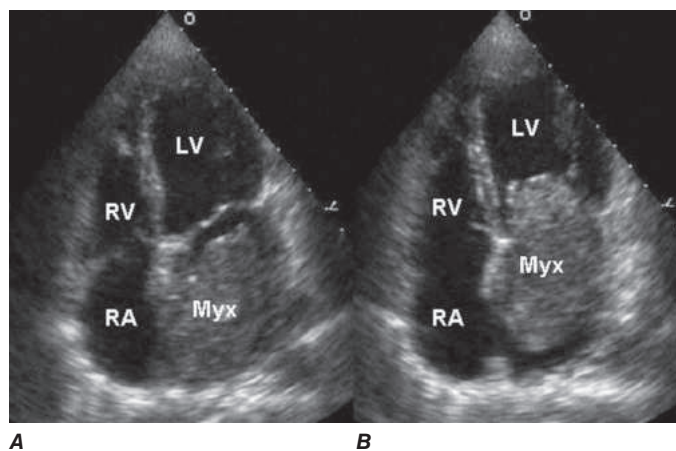


FIGURE 282-1 Transthoracic echocardiogram demonstrating a large atrial myxoma. The myxoma (Myx) fills the entire left atrium in systole (A) and prolapses across the mitral valve and into the left ventricle (LV) during diastole (B). RA, right atrium; RV, right ventricle. (Courtesy of Dr. Michael Tsang; with permission.)

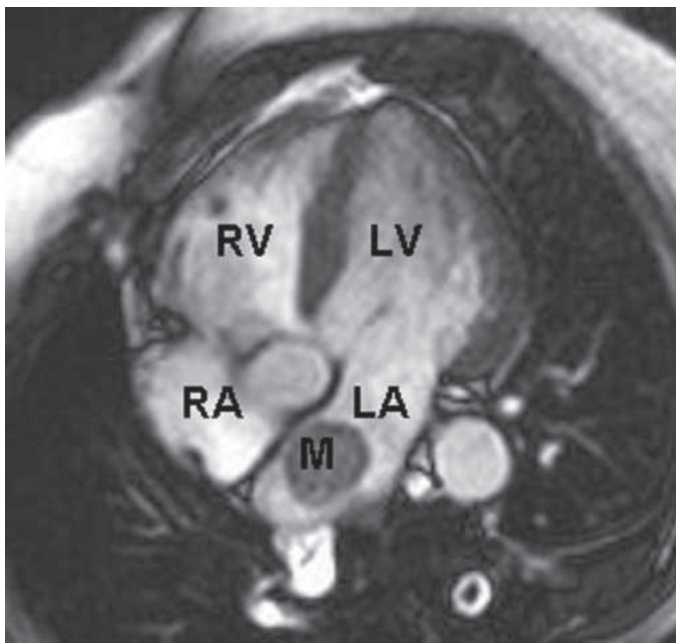


FIGURE 282-2 Cardiac magnetic resonance imaging demonstrating a rounded mass (M) within the left atrium (LA). Pathologic evaluation at the time of surgery revealed it to be an atrial myxoma. LV, left ventricle; RA, right atrium; RV, right ventricle.

Computed tomography (CT) and MRI may provide important additional information regarding size, shape, composition, and surface characteristics of the tumor (Fig. 282-2).

Although cardiac catheterization and angiography were previously performed routinely before tumor resection, they no longer are considered mandatory when adequate noninvasive information is available and other cardiac disorders (e.g., coronary artery disease) are not considered likely. Additionally, catheterization of the chamber from which the tumor arises carries the risk of tumor embolization. Because myxomas may be familial, echocardiographic screening of first-degree relatives is appropriate, particularly if the patient is young and has multiple tumors or features of a myxoma syndrome.

TREATMENT

Myxoma

Surgical excision using cardiopulmonary bypass is indicated regardless of tumor size and is generally curative. Myxomas recur in 12–22% of familial cases but in only 1–2% of sporadic cases. Tumor recurrence most likely results from multifocal lesions in the former setting and incomplete tumor resection in the latter.

Other Benign Tumors Cardiac *lipomas*, although relatively common, are usually incidental findings at postmortem examination; however, they may grow as large as 15 cm, may present as an abnormality of the cardiac silhouette on chest x-ray, and should be resected if they produce symptoms owing to mechanical interference with cardiac function, arrhythmias, or conduction disturbances. *Papillary fibroelastomas* are friable tumors with frond-like projections that are usually solitary and are the most common tumors of the cardiac valves. Although usually clinically silent, they can cause valve dysfunction and may embolize distally, resulting in transient ischemic attacks, stroke, or myocardial infarction. In general, these tumors should be resected even when asymptomatic, although a more conservative approach may be considered for small, right-sided lesions. *Rhabdomyomas* and *fibromas* are the most common cardiac tumors in infants and children and usually occur in the ventricles, where they may produce mechanical obstruction to blood flow, thereby mimicking valvular stenosis, CHF, restrictive or hypertrophic cardiomyopathy, or pericardial constriction. Rhabdomyomas are probably hamartomatous growths, are multiple in

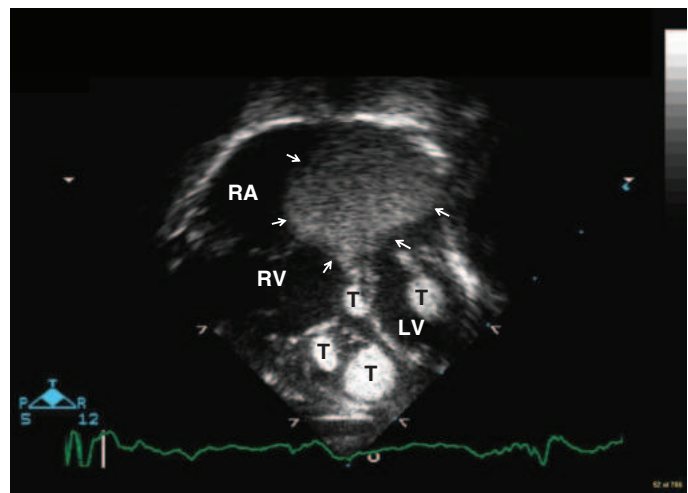


FIGURE 282-3 Transthoracic echocardiogram revealing multiple tumors (T) consistent with rhabdomyomas in a 1-day-old infant. The largest tumor (arrows) was located in the left antioventricular groove and measured 2 cm × 2 cm. LV, left ventricle; RA, right atrium; RV, right ventricle.

90% of cases, occur in ~50% of children with tuberous sclerosis, and are associated with mutations in the tumor-suppressor genes *TSC1* and *TSC2* (Fig. 282-3). These tumors have a tendency to regress completely or partially; only tumors that cause obstruction require surgical resection. Fibromas are usually single, universally ventricular in location, often calcified, and may be associated with mutations in the tumor-suppressor gene *PTCH1*. Fibromas tend to grow and cause arrhythmias and obstructive symptoms and should be completely resected when possible. *Paragangliomas* are rare chromaffin cell tumors that represent extra-adrenal pheochromocytomas. Most are located in the roof of the left atrium and can be identified on cardiac CT or MRI or with nuclear scanning using ^{131}I -metaiodobenzylguanidine. They are highly vascular and may be hormonally active, resulting in uncontrolled hypertension. Extensive surgical resection is usually required. *Hemangiomas* and *mesotheliomas* are generally small tumors, most often intramyocardial in location, and may cause atrioventricular (AV) conduction disturbances and even sudden death as a result of their propensity to develop in the region of the AV node. Other benign tumors arising from the heart include *teratoma*, *chemodectoma*, *neurilemoma*, and *granular cell myoblastoma*.

Malignant Tumors Almost all malignant primary cardiac tumors are sarcomas, which may be of several histologic types; angiosarcomas are the most common type in adults, whereas rhabdomyosarcomas are the most common type in children. In general, sarcomas are characterized by rapid progression that culminates in the patient's death within weeks to months from the time of presentation as a result of hemodynamic compromise, local invasion, or distant metastases. Almost one-third are metastatic at the time of initial diagnosis, usually involving the lungs. Sarcomas commonly involve the right side of the heart, are rapidly growing, frequently invade the pericardial space, and may obstruct the cardiac chambers or venae cavae. Sarcomas also may occur on the left side of the heart and may be mistaken for myxomas. Isolated cardiac lymphomas have been rarely described but more commonly occur in the context of systemic disease. They are more common in men and in the elderly; usually involve the right heart; may present with arrhythmias, syncope, CHF, or constitutional symptoms; and are usually of the large B-cell type.

TREATMENT

Malignant Tumors

The optimal therapy for cardiac sarcoma is complete resection, often with neoadjuvant and postoperative chemotherapy; however, at the time of presentation, many of these tumors have spread too extensively to allow for surgical excision. Although there are

scattered reports of palliation with radiotherapy and/or chemotherapy, the response of cardiac sarcomas to these therapies is generally poor. The one exception appears to be cardiac lymphosarcomas, which may respond to a combination of chemo- and radiotherapy. Primary cardiac lymphoma is the most chemotherapy-sensitive primary cardiac malignancy, with long-term survival achieved in ~40% of treated individuals.

TUMORS METASTATIC TO THE HEART

Metastatic cardiac tumors are much more common than primary cardiac tumors, and their incidence is likely to increase as the life expectancy of patients with various forms of malignant neoplasms is extended by more effective therapy and improved imaging modalities allow earlier identification of metastatic disease. Although cardiac metastases may occur with any tumor type, the relative incidence is especially high in malignant melanoma and, to a somewhat lesser extent, leukemia and lymphoma (Fig. 282-4). In absolute terms, the most common primary sites from which cardiac metastases originate are carcinoma of the breast and lung, reflecting the high incidence of these malignancies. Cardiac metastases almost always occur in the setting of widespread primary disease; most often, there is either primary or metastatic disease elsewhere in the thoracic cavity.

Cardiac metastases may occur via hematogenous or lymphangitic spread or by direct tumor invasion. While they generally manifest as small, firm nodules, diffuse infiltration also may occur, especially with sarcomas or hematologic neoplasms. The pericardium is most often involved, followed by myocardial involvement of any chamber and, rarely, by involvement of the endocardium or cardiac valves.

Cardiac metastases are clinically apparent only ~10% of the time, are usually not the cause of the patient's presentation, and rarely are the cause of death. The vast majority occur in the setting of a previously recognized malignant neoplasm. As with primary cardiac tumors, the clinical presentation reflects more the location and size of the tumor than its histologic type. When symptomatic, cardiac metastases may result in a variety of clinical features, including dyspnea, acute pericarditis, cardiac tamponade, ectopic tachyarrhythmias, heart block, and CHF. Importantly, many of these signs and symptoms may also result from myocarditis, pericarditis, or cardiomyopathy induced by radiotherapy or chemotherapy, and a high index of suspicion for cardiac involvement should be maintained for patients with malignant disease who develop these symptoms.

Electrocardiographic (ECG) findings are nonspecific but may reveal features consistent with pericarditis or may demonstrate low QRS voltage and electrical alternans in the setting of a large pericardial effusion. On chest x-ray, the cardiac silhouette is most often normal but may be enlarged or exhibit a bizarre contour. Echocardiography is useful for

identifying and assessing the significance of pericardial effusions and visualizing larger metastases, although CT and radionuclide imaging may define the tumor burden more clearly. Cardiac MRI offers superb image quality and plays a central role in the diagnostic evaluation of cardiac metastases and cardiac tumors in general. Pericardiocentesis may allow for a specific cytologic diagnosis in patients with malignant pericardial effusions with a reported sensitivity of 67–92%. Angiography is rarely necessary but may help to delineate discrete myocardial lesions.

TREATMENT

Tumors Metastatic to the Heart

Most patients with cardiac metastases have advanced malignant disease; thus, therapy is generally palliative and consists of controlling symptoms and treatment of the primary tumor. Symptomatic malignant pericardial effusions should be drained by pericardiocentesis. For patients with refractory or recurrent malignant pericardial effusion, the surgical creation of a pericardial window allowing for drainage of the effusion to the adjacent pleural or peritoneal space may prevent recurrent pericardial tamponade. Prolonged drainage (3–5 days) and concomitant instillation of a sclerosing agent (e.g., bleomycin) can be considered as a palliative measure in terminally ill patients. Given the overall poor prognosis of these patients, discussions regarding goals of care and involvement of palliative care services are often appropriate.

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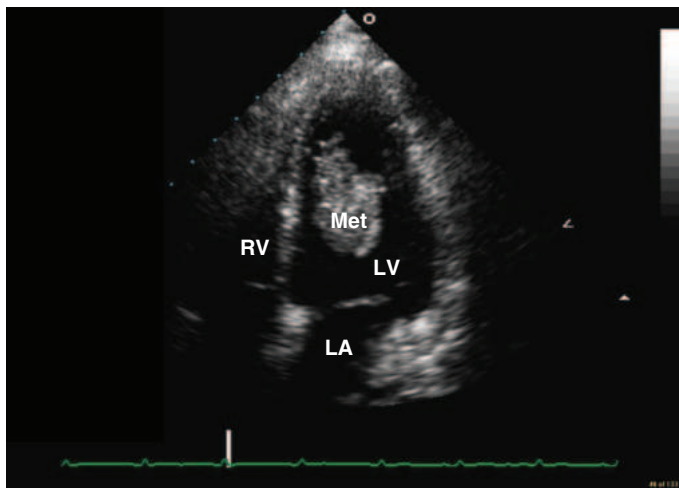


FIGURE 282-4 Large metastatic lesion (Met) in the left ventricle (LV) of a patient with diffusely metastatic bladder cancer. The mass arose from the interventricular septum and prolapsed into the aortic outflow tract during systole.

283 Cardiac Trauma

Alexandra R. Pipilas, Eric H. Awtry

CARDIAC TRAUMA

Traumatic cardiac injury may be caused by either penetrating or nonpenetrating trauma; the latter is often referred to as blunt cardiac injury (BCI). *Penetrating injuries* most often result from gunshot or knife wounds, and the site of entry is usually obvious. *Blunt cardiac injuries* most often occur during motor vehicle accidents, either from rapid deceleration or from impact of the chest, but can also result from falls from heights, crush injuries, blast injuries, violent assault, or significant physical contact during sporting events. Importantly, rapid deceleration following motor vehicle accidents may be associated with significant cardiac injury even in the absence of external signs of thoracic trauma.

BLUNT CARDIAC INJURY

Myocardial contusion is a nonspecific term that has been used to describe a broad spectrum of nonpenetrating cardiac injuries that

TABLE 283-1 Spectrum of Cardiac Abnormalities Following Blunt Cardiac Injury

ABNORMALITY	COMMENTS
ECG abnormalities	Sinus tachycardia, RBBB, heart block, ST-T wave abnormalities, atrial and ventricular arrhythmias
Elevated cardiac biomarkers	Troponin I or T are most specific
Focal wall motion abnormality or hematoma	Most commonly involving RV free wall, LV apex, and interventricular septum
Valvular insufficiency	Most commonly involving mitral and tricuspid valves and occasionally the aortic valve
Myocardial rupture	Ventricular septal defect or free wall rupture
Coronary artery injury	Most commonly involving the LAD; usually presents as STEMI
Pericardial effusion and tamponade	Resulting from free wall rupture or coronary artery laceration

Abbreviations: ECG, electrocardiogram; LAD, left anterior descending coronary artery; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle; STEMI, ST-segment elevation myocardial infarction.

result in abnormalities on electrocardiogram (ECG), elevation in cardiac biomarkers, and acute structural cardiac abnormalities (**Table 283-1**). Importantly, the cardiac injury may initially be overlooked in trauma patients as the clinical focus is directed toward other, more obvious injuries. Unfortunately, there is no one sign or symptom that confirms the diagnosis of BCI, and clinical, laboratory, and radiographic findings may be nonspecific in the setting of significant trauma. The physical examination may be challenging in the setting of chest wall injury; however, patients should be carefully examined to detect pericardial rubs, cardiac murmurs, and evidence of pericardial tamponade (**Chap. 281**). The mechanism of injury and the presence of other chest trauma should be considered when determining the index of suspicion for BCI; however, there is no proven association between sternal or rib fractures and the presence of BCI, and significant cardiac injury may be present in the absence of chest wall abnormalities.

Chest pain is common following thoracic trauma, and while it can indicate cardiac ischemia or pericardial injury, it often reflects musculoskeletal trauma. Nonetheless, myocardial necrosis may occur as a direct result of the blunt injury or as a result of traumatic coronary laceration, dissection, or thrombosis. The injured myocardium is pathologically similar to infarcted myocardium and may be associated with atrial or ventricular arrhythmias, conduction disturbances including bundle branch and atrioventricular (AV) nodal block, or abnormalities on ECG resembling those of infarction or pericarditis. Thus, it is important to obtain an ECG in all patients presenting with chest trauma.

Serum creatine kinase, myocardial band (CK-MB) isoenzyme levels are increased in ~20% of patients who experience blunt chest trauma but may be falsely elevated in the presence of massive skeletal muscle injury and should not be relied upon to confirm the diagnosis of BCI in the setting of trauma. Cardiac troponin levels are more specific for identifying cardiac damage; patients with normal serial troponin levels after chest trauma are very unlikely to have sustained cardiac injury. When combined with a normal ECG, a normal troponin level at 6–8 h after chest trauma essentially excludes BCI. Echocardiography is the most useful modality for the detection of structural and functional sequelae of BCI, including regional wall motion abnormalities (most commonly involving the right ventricle, interventricular septum, or left ventricular apex), pericardial effusion, valvular dysfunction, and ventricular or ventricular septal rupture. A transthoracic echocardiogram (TTE) should be performed in all patients with suspected BCI, especially in those with an abnormal ECG, elevated troponin, or hemodynamic instability; transesophageal echocardiography should be considered for patients in whom adequate TTE images cannot be obtained.

Traumatic rupture of the cardiac valves or their supporting structures, most commonly of the tricuspid or aortic valves, leads to acute valvular incompetence. This complication is usually heralded by the development of a loud murmur, may be associated with rapidly

progressive heart failure, and can be diagnosed by either TTE or transesophageal echocardiography. BCI may also result in dissection, occlusion, or laceration of the coronary arteries. ST elevation may be seen on the ECG, and prompt intervention is often required.

The most serious consequence of nonpenetrating cardiac injury is myocardial rupture. Free wall rupture may result in hemopericardium and tamponade while a ventricular septal rupture can result in significant intracardiac shunting. Although generally fatal, up to 40% of patients with cardiac rupture have been reported to survive long enough to reach a specialized trauma center. Hemopericardium also may result from traumatic rupture of a pericardial vessel or a coronary artery. Additionally, pericarditis and/or pericardial effusion may develop weeks or even months after blunt chest trauma as a manifestation of the post-cardiac injury syndrome, an inflammatory condition that resembles the postpericardiotomy syndrome (**Chap. 281**).

Blunt, nonpenetrating, often innocent-appearing injuries to the chest may trigger ventricular fibrillation even in the absence of structural myocardial damage. This syndrome, referred to as *commotio cordis*, occurs most often in adolescents during sporting events (e.g., baseball, hockey, football, and lacrosse) and is an electrical phenomenon that probably results from an impact to the chest wall overlying the heart during the susceptible phase of repolarization (just before the peak of the T wave). Survival depends on prompt defibrillation. Sudden emotional or physical trauma, even in the absence of direct cardiac trauma, may precipitate a transient catecholamine-mediated cardiomyopathy referred to as *takotsubo syndrome* or *apical ballooning syndrome* (**Chaps. 266–270**).

Rupture or transection of the aorta, usually just above the aortic valve or at the site of the tethering ligamentum arteriosum, is a common consequence of nonpenetrating chest trauma and is the most common vascular deceleration injury. The clinical presentation may be similar to that of aortic dissection (**Chap. 291**); the arterial pressure and pulse amplitude may be increased in the upper extremities and decreased in the lower extremities, and chest x-ray may reveal mediastinal widening. Aortic rupture into the left thoracic space is almost universally fatal; however, the rupture may occasionally be contained by the aortic adventitia, resulting in a false, or *pseudo*-, aneurysm that may be discovered months or years after the initial injury.

TREATMENT

Blunt Cardiac Injury

The treatment of BCI depends on the specific injury sustained. Hemodynamically stable patients with a normal ECG and normal serial troponin levels are at low risk for BCI and usually do not require hospital admission for cardiac issues. Patients with an abnormal ECG, including those with conduction disturbances, and/or elevated troponin but normal echocardiogram usually warrant 24–48 h of telemetry monitoring; however, other specific cardiac treatment is not usually required in the absence of the development of arrhythmias, as conduction disturbances are often transient. Patients with mechanical complications (acute valvular insufficiency, myocardial rupture) require urgent operative correction.

■ PENETRATING CARDIAC INJURY

Penetrating injuries of the heart produced by knife or bullet wounds usually result in rapid clinical deterioration and frequently in death as a result of hemopericardium/pericardial tamponade or massive hemorrhage. Nonetheless, up to half of such patients may survive long enough to reach a specialized trauma center if immediate resuscitation is performed. Prognosis in these patients relates to the mechanism of injury, the specific cardiac chamber(s) involved, and their clinical condition at presentation. In general, gunshot wounds are associated with a higher mortality than are knife wounds. Twenty percent of shooting victims survive versus up to 65% of stabbing victims. This is likely in part because ballistic wounds are more frequently associated with multichamber cardiac injury. As a result of its anterior position in the chest, the right ventricle (RV) is the most frequently injured cardiac chamber,

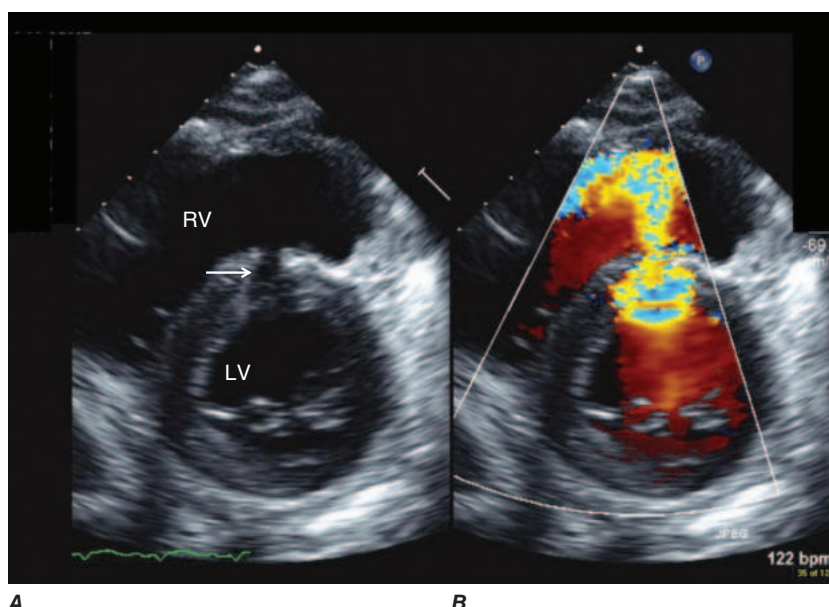


FIGURE 283-1 Transthoracic echocardiogram demonstrating a traumatic ventricular septal defect. The patient underwent emergent repair of the right ventricle following a self-inflicted stab wound to the chest. Subsequent two-dimensional imaging (**A**) revealed a laceration of the interventricular septum (arrow) with color flow Doppler (**B**) demonstrating prominent left-to-right shunting across the defect. LV, left ventricle; RV, right ventricle.

followed by the left ventricle (LV); isolated atrial injury is uncommon. Some studies suggest that RV injuries may be associated with a better prognosis than LV injuries, and most reports indicate that multichamber involvement carries a worse prognosis than single-chamber injury. Patients who are in hemodynamic collapse at presentation to the emergency department have a particularly poor prognosis with a mortality rate approaching 90%, whereas ~75% of patients who are stable enough to be brought to the operating room will survive.

Cardiac perforation of the right atrium, the RV free wall, or the interventricular septum may occur as a complication of cardiac procedures including placement of central venous/intracardiac catheters, insertion of pacemaker/defibrillator leads, or performance of RV endomyocardial biopsies; and coronary arterial perforation can occur during deployment of intracoronary stents. These iatrogenic injuries are associated with a better prognosis than are other forms of penetrating cardiac trauma, likely related to a more limited degree of cardiac injury and the rapid availability of corrective therapies.

Traumatic rupture of a great vessel from penetrating injury is usually associated with hemothorax and, less often, hemopericardium, both of which are associated with significant mortality. Local hematoma formation may compress adjacent vessels and produce ischemic symptoms, and arteriovenous fistulas may develop, occasionally resulting in high-output heart failure.

Some patients with penetrating chest injuries are hemodynamically stable at presentation and without symptoms to suggest cardiac injury; however, as many as 20% of these patients will have occult penetrating cardiac trauma. As a result, there should always be a high index of suspicion for cardiac injury in any patient with penetrating chest trauma, irrespective of clinical stability. TTE should be performed in all of these patients to assess for the presence of pericardial effusion or hematoma.

Occasionally, patients who survive penetrating cardiac injuries may subsequently present days or weeks later with a new cardiac murmur or heart failure as a result of mitral or tricuspid regurgitation or an intracardiac shunt (i.e., ventricular or atrial septal defect, aortopulmonary fistula, or coronary arteriovenous fistula) that was undetected at the time of the initial injury or developed subsequently (**Fig. 283-1**). Therefore, trauma patients should be examined carefully several weeks after the injury. If a mechanical complication is suspected, it can be confirmed by echocardiography or cardiac catheterization.

TREATMENT

Penetrating Cardiac Injury

Penetrating cardiac injury associated with hemodynamic instability is a surgical emergency and requires immediate resuscitative measures including endotracheal intubation, establishment of large-bore intravenous access to facilitate massive volume resuscitation, and immediate thoracotomy to allow for pericardial drainage and repair of cardiac injuries. Occasionally, cross-clamping of the descending aorta is required to perfuse the heart and brain preferentially until hemodynamic stability can be achieved. Hemodynamically stable patients in whom echocardiography reveals even a small pericardial effusion require urgent surgical exploration to evaluate for occult cardiac perforation. Pericardiocentesis may be lifesaving in patients with tamponade but is usually only a temporizing measure while awaiting definitive surgical therapy. In some survivors of penetrating cardiac injury, the pericardial hemorrhage predisposes to the development of constriction (**Chap. 281**), which may require surgical decortication.

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Section 5 Coronary and Peripheral Vascular Disease

284 Ischemic Heart Disease

Robert P. Giugliano, Elliott M. Antman, Joseph Loscalzo

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery. This chapter focuses on the chronic manifestations and treatment of IHD (sometimes referred to as chronic coronary disease or chronic coronary syndrome), while the subsequent chapters address the acute phases of IHD.

■ EPIDEMIOLOGY AND GLOBAL TRENDS

IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. IHD is the most common, serious, chronic, life-threatening illness in the United States, where 20.5 million persons have IHD. Although there is regional variation, ~3–4% of the population has sustained a myocardial infarction. Genetic factors, a high-fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD. In the United States and Western Europe, IHD is growing among low-income groups, but primary prevention has delayed the disease to later in life across socioeconomic groups. Despite these sobering statistics, it is worth noting that epidemiologic data show a decline in the rate of deaths due to IHD, about half of which is attributable to treatments and half to prevention by risk factor modification.

Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD. These trends are occurring in

the general context of population growth and as a result of the increase in the average age of the world's population. With urbanization in countries with emerging economies and a growing middle class, elements of the energy-rich Western diet are being adopted. As a result, the prevalence of risk factors for IHD and the prevalence of IHD itself are both increasing rapidly, so that in analyses of the global burden of disease, there is a shift from communicable to noncommunicable diseases, and it is estimated that globally over 200 million people live with IHD. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India and the Middle East. IHD is a major contributor to the number of disability-adjusted life-years (DALYs) experienced globally.

■ PATHOPHYSIOLOGY

Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. In normal conditions, for any given level of a demand for oxygen, the myocardium will control the supply of oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction. The major determinants of myocardial oxygen demand (MVO₂) are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood flow. Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries: (1) large epicardial arteries (Resistance 1 = R₁), (2) prearteriolar vessels (R₂), and (3) arteriolar and intramyocardial capillary vessels (R₃). In the absence of significant flow-limiting atherosclerotic obstructions, R₁ is trivial; the major determinant of coronary resistance is found in R₂ and R₃ (Fig. 284-1). The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate a great capacity for dilation (R₂ and R₃ decrease). The changing oxygen needs of the heart with exercise and emotional stress affect coronary

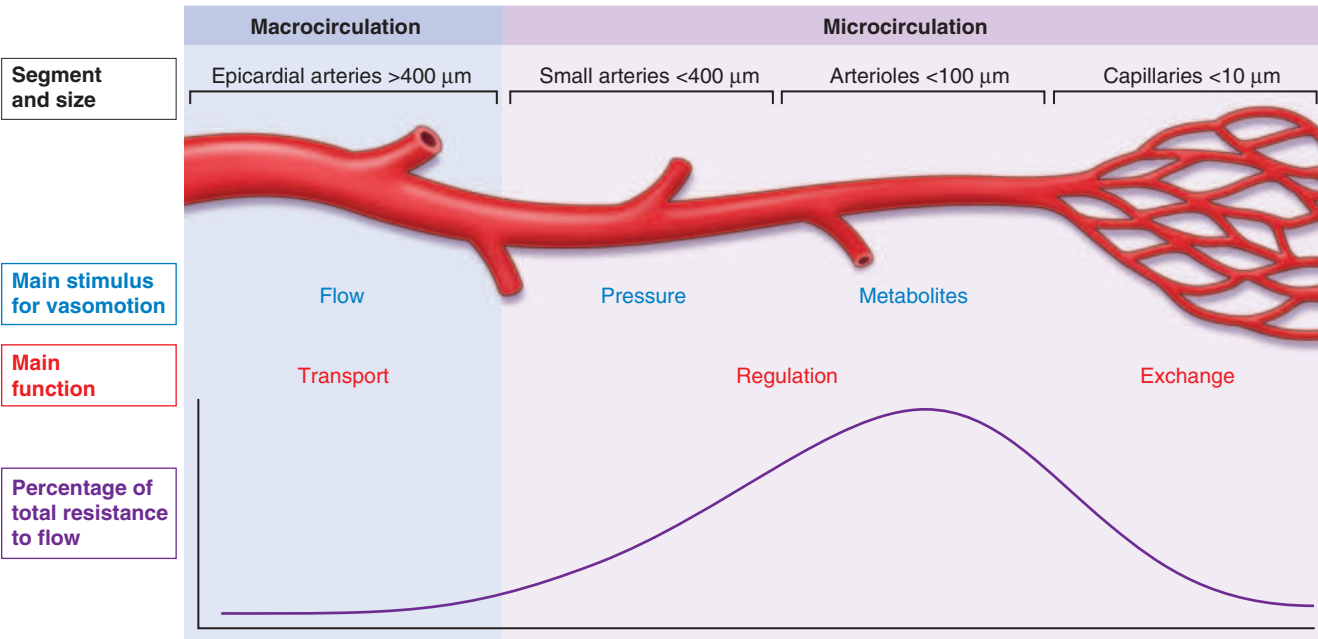


FIGURE 284-1 Macrocirculation and microcirculation across segments and sizes of the arteries. The location and size of the arteries supplying blood to the heart is shown at the top. Vasomotion of the arterial segments occurs in response to the stimuli shown. The main function of each of the arterial segments is shown next, followed by a depiction of the relative resistance to antegrade flow. (Adapted from J Knuuti et al: 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 41:407, 2020/.)

vascular resistance and, in this manner, regulate the supply of oxygen and substrate to the myocardium (*metabolic regulation*). The coronary resistance vessels also adapt to physiologic alterations in blood pressure to maintain coronary blood flow at levels appropriate to myocardial needs (*autoregulation*).

By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for more coronary flow occurs. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow also can be limited by spasm (see vasospastic angina in [Chap. 285](#)), arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities such as the origin of the left anterior descending coronary artery from the pulmonary artery may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults.

Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased and particularly when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy (LVH) due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely owing to subendocardial ischemia ([Chap. 272](#)). A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself but may lower the threshold for ischemia in patients with moderate coronary obstruction.

Not infrequently, two or more causes of ischemia coexist in a patient, such as an increase in oxygen demand due to LVH secondary to hypertension and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia. Abnormal constriction or failure of normal dilation of the coronary resistance vessels also can cause ischemia. When it causes angina, this condition is referred to as *microvascular angina*.

CORONARY ATHEROSCLEROSIS

Epicardial coronary arteries are the major site of atherosclerotic disease. The major risk factors for atherosclerosis (high levels of plasma low-density lipoprotein [LDL], cigarette smoking, hypertension, and diabetes mellitus) vary in their relative impact on disturbing the normal functions of the vascular endothelium. These functions include local control of vascular tone, maintenance of an antithrombotic surface, and control of inflammatory cell adhesion and diapedesis. The loss of these defenses leads to inappropriate constriction, luminal thrombus formation, and abnormal interactions between blood cells, especially monocytes and platelets, and the activated vascular endothelium. Functional changes in the vascular milieu ultimately result in the subintimal collections of fat, smooth muscle cells, fibroblasts, and intercellular matrix that define the atherosclerotic plaque. Rather than viewing atherosclerosis strictly as a vascular problem, it is useful to consider it in the context of alterations in the nature of the circulating blood (hyperglycemia; increased concentrations of LDL cholesterol, tissue factor, fibrinogen, von Willebrand factor, coagulation factor VII, and platelet microparticles). The combination of a “vulnerable vessel” in a patient with “vulnerable blood” promotes a state of hypercoagulability and hypofibrinolysis. This is especially true in patients with diabetes mellitus.

Atherosclerosis develops at irregular rates in different segments of the epicardial coronary tree and leads eventually to segmental reductions in cross-sectional area, i.e., plaque formation. There is also a predilection for atherosclerotic plaques to develop at sites of increased turbulence in coronary flow, such as at branch points in the epicardial arteries. When a stenosis reduces the diameter of an epicardial artery by 50%, there is a limitation of the ability to increase flow to meet increased myocardial demand. When the diameter is reduced by ~80%, blood flow at rest may be reduced, and further minor decreases in the stenotic orifice area can reduce coronary flow dramatically to cause myocardial ischemia at rest or with minimal stress.

Segmental atherosclerotic narrowing of epicardial coronary arteries is caused most commonly by the formation of a plaque, which is subject to rupture or erosion of the cap separating the plaque from

the bloodstream. Upon exposure of the plaque contents to blood, two important and interrelated processes are set in motion: (1) platelets are activated and aggregate, and (2) the coagulation cascade is activated, leading to deposition of fibrin strands. A thrombus composed of platelet aggregates and fibrin strands traps red blood cells and can reduce coronary blood flow, leading to the clinical manifestations of myocardial ischemia.

The location of the obstruction influences the quantity of myocardium rendered ischemic and determines the severity of the clinical manifestations. Thus, critical obstructions in vessels, such as the left main coronary artery and the proximal left anterior descending coronary artery, are particularly hazardous. Chronic severe coronary narrowing and myocardial ischemia frequently are accompanied by the development of collateral vessels, especially when the narrowing develops gradually. When well developed, such vessels can by themselves provide sufficient blood flow to sustain the viability of the myocardium at rest but not during conditions of increased demand.

With progressive worsening of a stenosis in a proximal epicardial artery, the distal resistance vessels (when they function normally) dilate to reduce vascular resistance and maintain coronary blood flow. A pressure gradient develops across the proximal stenosis, and poststenotic pressure falls. When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction. In these circumstances, ischemia, manifest clinically by angina or electrocardiographically by ST-segment deviation, can be precipitated by increases in myocardial oxygen demand caused by physical activity, emotional stress, and/or tachycardia. Changes in the caliber of the stenosed coronary artery resulting from physiologic vasomotion, loss of endothelial control of dilation (as occurs in atherosclerosis), pathologic spasm (vasospastic angina), or small platelet-rich plugs also can upset the critical balance between oxygen supply and demand and thereby precipitate myocardial ischemia.

■ EFFECTS OF ISCHEMIA

During episodes of inadequate perfusion caused by coronary atherosclerosis, myocardial tissue oxygen tension falls and may cause transient disturbances of the mechanical, biochemical, and electrical functions of the myocardium ([Fig. 284-2](#)). Coronary atherosclerosis is a focal process that usually causes nonuniform ischemia. During ischemia, regional disturbances of ventricular contractility cause segmental hypokinesia, akinesia, or, in severe cases, bulging (dyskinesia), which can reduce myocardial pump function.

The abrupt development of severe ischemia, as occurs with total or subtotal coronary occlusion, is associated with near instantaneous failure of normal muscle relaxation and then diminished contraction. The relatively poor perfusion of the subendocardium causes more intense ischemia of this portion of the wall (compared with the subepicardial region). Ischemia of large portions of the ventricle causes transient left ventricular (LV) failure, and if the papillary muscle apparatus is involved, mitral regurgitation can occur. When ischemia is transient, it may be associated with angina pectoris; when it is prolonged, it can lead to myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction ([Chap. 286](#)).

A wide range of abnormalities in cell metabolism, function, and structure underlie these mechanical disturbances during ischemia. The normal myocardium metabolizes fatty acids and glucose to carbon dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is converted to lactate; intracellular pH is reduced, as are the myocardial stores of high-energy phosphates, i.e., ATP and creatine phosphate. Impaired cell membrane function leads to the leakage of potassium and the uptake of sodium by myocytes as well as an increase in cytosolic calcium. The severity and duration of the imbalance between myocardial oxygen supply and demand determine whether the damage is reversible (≤ 20 min for total occlusion in the absence of collaterals) or permanent, with subsequent myocardial necrosis (>20 min).

Ischemia also causes characteristic changes in the electrocardiogram (ECG) such as repolarization abnormalities, as evidenced by inversion

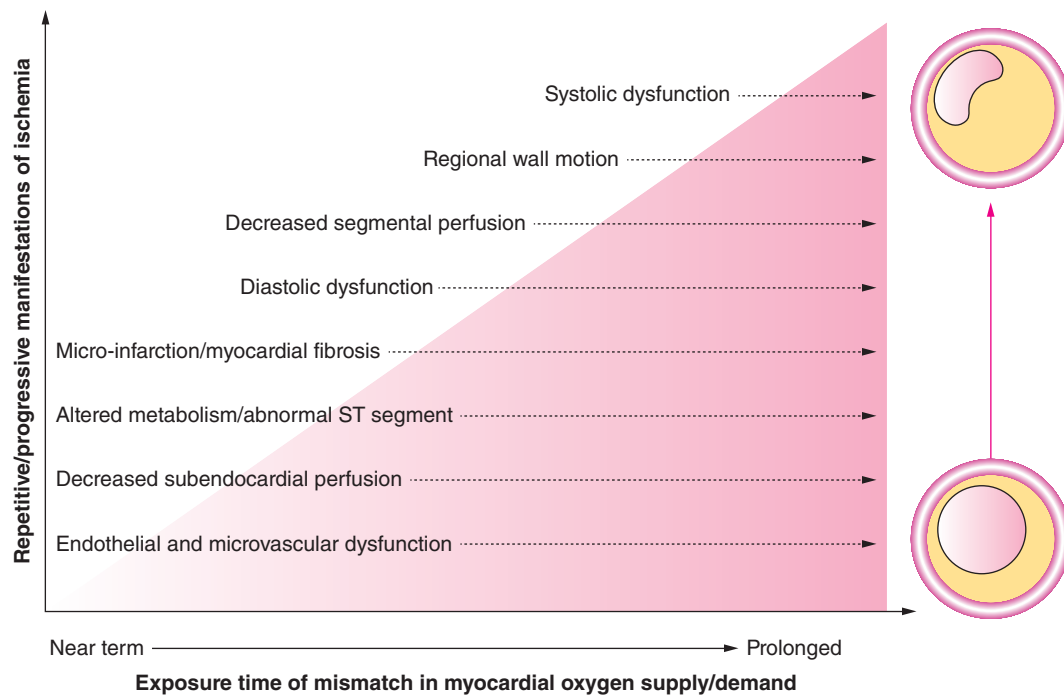


FIGURE 284-2 Cascade of mechanisms and manifestations of ischemia. (Reproduced with permission from LJ Shaw et al: *Women and ischemic heart disease: Evolving knowledge*. *J Am Coll Cardiol* 54:1561, 2009.)

of T waves and, when more severe, displacement of ST segments (Chap. 247). Transient T-wave inversion probably reflects nontransmural, intramyocardial ischemia; transient ST-segment depression often reflects patchy subendocardial ischemia; and ST-segment elevation is thought to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, which may lead to isolated ventricular premature beats or even ventricular tachycardia or ventricular fibrillation (Chaps. 261 and 262). Most patients who die suddenly from IHD do so as a result of ischemia-induced ventricular tachyarrhythmias (Chap. 317).

■ ASYMPTOMATIC VERSUS SYMPTOMATIC IHD

Although the prevalence is decreasing, postmortem studies of accident victims and military casualties in Western countries show that coronary atherosclerosis can begin before age 20 and is present among adults who were asymptomatic during life. Exercise stress tests in asymptomatic persons may show evidence of silent myocardial ischemia, i.e., exercise-induced ECG changes not accompanied by angina pectoris; coronary angiographic studies of such persons may reveal coronary artery plaques and previously unrecognized obstructions (Chap. 249). Coronary artery calcifications (CACs) may be seen on computed tomography (CT) images of the heart, can be quantified in a CAC score, and may be used as adjunctive information to support a diagnosis of IHD. However, they should not be used as the primary screening modality or as the isolated basis on which to formulate therapeutic decisions. (See further discussion below.) Postmortem examination of patients with such obstructions without a history of clinical manifestations of myocardial ischemia often shows macroscopic scars secondary to myocardial infarction in regions supplied by diseased coronary arteries, with or without collateral circulation. According to population studies, ~25% of patients who survive acute myocardial infarction may not come to medical attention, and these patients have the same adverse prognosis as do those who present with the classic clinical picture of acute myocardial infarction (Chap. 286). Sudden death may be unheralded and is a common presenting manifestation of IHD (Chap. 317).

Patients with IHD also can present with cardiomegaly and heart failure secondary to ischemic damage of the LV myocardium that may have caused no symptoms before the development of heart failure; this condition is referred to as *ischemic cardiomyopathy*. In contrast to the asymptomatic phase of IHD, the symptomatic phase is characterized

by chest discomfort due to either angina pectoris or acute myocardial infarction (Chap. 286). Having entered the symptomatic phase, the patient may exhibit a stable or progressive course, revert to the asymptomatic stage, or die suddenly.

STABLE ANGINA PECTORIS

This episodic clinical syndrome is a result of transient myocardial ischemia. Various diseases that cause myocardial ischemia and the numerous forms of discomfort with which it may be confused are discussed in Chap. 15. Males constitute ~70% of all patients with angina pectoris and an even greater proportion of those aged <50 years. It is, however, important to note that descriptions of angina pectoris in women may be different from that in men.

■ HISTORY

The typical patient with angina is a man >50 years or a woman >60 years of age who complains of episodes of chest discomfort, usually described as heaviness, pressure, squeezing, smothering, or choking and only rarely as frank pain. When the patient is asked to localize the sensation, they typically place a hand over the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort (Levine's sign). Angina is usually crescendo-decrescendo in nature (typically with the severity of the discomfort not at its most intense level at the outset of symptoms), typically lasts 2–5 min, and can radiate to either shoulder and to both arms (especially the ulnar aspects of the forearm and hand). It also can arise in or radiate to the back, interscapular region, root of the neck, jaw, teeth, and epigastrium. Angina is rarely localized below the umbilicus or above the mandible. A useful finding in assessing a patient with chest discomfort is the fact that myocardial ischemic discomfort does not radiate to the trapezius muscles; that radiation pattern is more typical of pericarditis.

Although episodes of angina typically are caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger, fright, or frustration) and are relieved by rest, they also may occur at rest and while the patient is recumbent (angina decubitus). The patient may be awakened at night by typical chest discomfort and dyspnea. Nocturnal angina may be due to episodic tachycardia, diminished oxygenation as the respiratory pattern changes during sleep, or expansion of the intrathoracic blood volume that occurs with recumbency; the latter causes an increase in cardiac size (end-diastolic volume), wall

tension, and myocardial oxygen demand that can lead to ischemia and transient LV failure.

The threshold for the development of angina pectoris may vary by time of day and emotional state. Many patients report a fixed threshold for angina, occurring predictably at a certain level of activity, such as climbing two flights of stairs at a normal pace. In these patients, coronary stenosis and myocardial oxygen supply are fixed, and ischemia is precipitated by an increase in myocardial oxygen demand; they are said to have stable exertional angina. In other patients, the threshold for angina may vary considerably within any particular day and from day to day. In such patients, variations in myocardial oxygen supply, most likely due to changes in coronary vasomotor tone, may play an important role in defining the pattern of angina. A patient may report symptoms upon minor exertion in the morning yet by midday be capable of much greater effort without symptoms. Angina may also be precipitated by unfamiliar circumstances, a heavy meal, exposure to cold, or a combination of these factors.

Exertional angina typically is relieved in 1–5 min by slowing or ceasing activities and even more rapidly by rest and sublingual nitroglycerin (see below). Indeed, the diagnosis of angina should be suspect if it does not respond to the combination of these measures. The severity of angina can be conveniently summarized by the Canadian Cardiac Society functional classification (Table 284-1). Its impact on the patient's functional capacity can be described by using the New York Heart Association functional classification (Table 284-1).

Sharp, fleeting chest pain or a prolonged, dull ache localized to the left submammary area is rarely due to myocardial ischemia. However, especially in women and patients with diabetes mellitus, angina pectoris may be atypical in location and not strictly related to provoking factors. In addition, this symptom may exacerbate and remit over days, weeks, or months. Its occurrence can be seasonal, occurring more

frequently in the winter in temperate climates. Anginal “equivalents” are symptoms of myocardial ischemia other than angina. They include dyspnea, nausea, fatigue, and faintness and are more common in the elderly and in patients with diabetes mellitus.

Systematic questioning of a patient with suspected IHD is important to uncover the features of an unstable syndrome associated with increased risk, such as angina occurring with less exertion than in the past, occurring at rest, or awakening the patient from sleep. Since coronary atherosclerosis often is accompanied by similar lesions in other arteries, a patient with angina should be questioned and examined for peripheral arterial disease (intermittent claudication [Chap. 292]), stroke, or transient ischemic attacks (Chap. 437). It is also important to uncover a family history of premature IHD (<55 years in first-degree male relatives and <65 years in female relatives) and the presence of diabetes mellitus, hyperlipidemia, hypertension, cigarette smoking, and other risk factors for coronary atherosclerosis.

The history of typical angina pectoris establishes the diagnosis of IHD until proven otherwise. Given the importance of the history, clinicians should move beyond unstructured interviews with the patient and consider using a validated questionnaire (e.g., Seattle Angina Questionnaire) to establish the presence and severity of IHD. The coexistence of advanced age, male sex, the postmenopausal state, and risk factors for atherosclerosis increases the likelihood of hemodynamically significant coronary disease. A particularly challenging problem is the evaluation and management of patients with persistent ischemic-type chest discomfort but no flow-limiting obstructions in their epicardial coronary arteries. This situation arises more often in women than in men. Potential etiologies include microvascular coronary disease (detectable on coronary reactivity testing in response to vasoactive agents such as intracoronary adenosine, acetylcholine, and nitroglycerin) and abnormal cardiac nociception. Treatment of microvascular coronary disease should focus on efforts to improve endothelial function, including nitrates, beta blockers, calcium antagonists, statins, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Abnormal cardiac nociception is more difficult to manage and may be ameliorated in some cases by imipramine.

■ PHYSICAL EXAMINATION

The physical examination is often normal in patients with stable angina when they are asymptomatic. However, because of the increased likelihood of IHD in patients with diabetes and/or peripheral or cerebrovascular arterial disease, clinicians should search for evidence of atherosclerotic disease at other sites, such as an abdominal aortic aneurysm, carotid arterial bruits, and diminished arterial pulses in the lower extremities. The physical examination also should include a search for evidence of risk factors for atherosclerosis such as xanthelasma and xanthomas. Evidence for peripheral and cerebrovascular arterial disease should be sought by evaluating the pulse contour at multiple locations and comparing the blood pressure between the arms and between the arms and the legs (ankle-brachial index). Examination of the fundi may reveal an increased light reflex and arteriovenous nicking as evidence of hypertension. There also may be signs of anemia, thyroid disease, and nicotine stains on the fingertips from cigarette smoking.

Palpation may reveal cardiac enlargement and abnormal contraction of the cardiac impulse (LV dyskinesia). Auscultation can uncover arterial bruits, a third and/or fourth heart sound, and, if acute ischemia or previous infarction has impaired papillary muscle function, an apical systolic murmur due to mitral regurgitation. These auscultatory signs are best appreciated with the patient in the left lateral decubitus position. Aortic stenosis, aortic regurgitation (Chap. 272), pulmonary hypertension (Chap. 294), and hypertrophic cardiomyopathy (Chaps. 266–270) must be excluded, since these disorders may cause angina in the absence of coronary atherosclerosis. Examination during an anginal attack is useful, since ischemia can cause transient LV failure with the appearance of a third and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema. Tenderness of the chest wall, localization of the discomfort with a single fingertip on the chest, or reproduction of the pain with palpation of the

TABLE 284-1 Cardiovascular Disease Classification Chart

CLASS	NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION	CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION
I	Patients have cardiac disease but <i>without</i> the resulting <i>limitations</i> of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, <i>does not cause angina</i> . Angina present with strenuous or rapid or prolonged exertion at work or recreation.
II	Patients have cardiac disease resulting in <i>slight limitation</i> of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	<i>Slight limitation</i> of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
III	Patients have cardiac disease resulting in <i>marked limitation</i> of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	<i>Marked limitation</i> of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs at normal pace.
IV	Patients have cardiac disease resulting in <i>inability</i> to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	<i>Inability</i> to carry on any physical activity without discomfort—anginal syndrome <i>may</i> be present at rest.

Source: Reproduced with permission from L Goldman et al: Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. *Circulation* 64:1227, 1981.

chest makes it unlikely that the pain is caused by myocardial ischemia. A protuberant abdomen may indicate that the patient has the metabolic syndrome and is at increased risk for atherosclerosis.

■ LABORATORY EXAMINATION

Although the diagnosis of IHD can be made with a high degree of confidence from the history and physical examination, a number of simple laboratory tests can be helpful. The urine should be examined for evidence of diabetes mellitus and renal disease (including microalbuminuria) since these conditions accelerate atherosclerosis. Similarly, examination of the blood should include measurements of lipids (cholesterol—total, LDL, high-density lipoprotein [HDL]—triglycerides, and lipoprotein (a)), glucose (hemoglobin A_{1c}), creatinine, hematocrit, and, if indicated based on the physical examination, thyroid function. A chest x-ray may be helpful in demonstrating the consequences of IHD, i.e., cardiac enlargement, ventricular aneurysm, or signs of heart failure. These signs can support the diagnosis of IHD and are important in assessing the degree of cardiac damage. Evidence exists that an elevated level of high-sensitivity C-reactive protein (CRP) (specifically, between 1 and 3 mg/L) is an independent risk factor for IHD and may be useful in therapeutic decision-making about the initiation of hypolipidemic treatment. The major benefit of high-sensitivity CRP is in reclassifying the risk of IHD in patients in the “intermediate” risk category on the basis of traditional risk factors.

■ ELECTROCARDIOGRAM

A 12-lead ECG recorded at rest may be normal in patients with typical angina pectoris, but there may also be signs of an old myocardial infarction (Chap. 247). Although repolarization abnormalities, i.e., ST-segment and T-wave changes, as well as LVH and disturbances of cardiac rhythm or intraventricular conduction, are suggestive of IHD, they are nonspecific, since they also can occur in pericardial, myocardial, and valvular heart disease or, in the case of the former, transiently with anxiety, changes in posture, drugs, or esophageal disease. The presence of LVH is a significant indication of increased risk of adverse outcomes from IHD. Of note, even though LVH and cardiac rhythm disturbances are nonspecific indicators of the development of IHD, they may be contributing factors to episodes of angina in patients in whom IHD has developed as a consequence of conventional risk factors. Dynamic ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific.

■ STRESS TESTING

Electrocardiographic The most widely used test for both the diagnosis of IHD and the estimation of risk and prognosis involves recording of the 12-lead ECG before, during, and after exercise, usually on a treadmill (Fig. 284-3). The test consists of a standardized incremental increase in external workload (Table 284-2) while symptoms, the ECG, and arm blood pressure are monitored. Exercise duration is usually symptom-limited, and the test is discontinued upon evidence of chest discomfort, severe shortness of breath, dizziness, severe fatigue, ST-segment depression >0.2 mV (2 mm), a fall in systolic blood pressure >10 mmHg, or the development of a ventricular tachyarrhythmia. This test is used to discover any limitation in exercise performance, detect typical ECG signs of myocardial ischemia, and establish their relationship to chest discomfort. The ischemic ST-segment response generally is defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 s (Fig. 284-2). Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Although T-wave abnormalities, conduction disturbances, and ventricular arrhythmias that develop during exercise should be noted, they are also not diagnostic. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered nondiagnostic.

In interpreting ECG stress tests, the probability that coronary artery disease (CAD) exists in the patient or population under study (i.e., pretest probability) should be considered. A positive result on exercise indicates that the likelihood of CAD is 98% in males who are

>50 years with a history of typical angina pectoris and who develop chest discomfort during the test. The likelihood decreases if the patient has atypical or no chest pain by history and/or during the test.

The incidence of false-positive tests is significantly increased in patients with low probabilities of IHD, such as asymptomatic men age <40 or premenopausal women with no risk factors for premature atherosclerosis. It is also increased in patients taking cardioactive drugs, such as digitalis and antiarrhythmic agents, and in those with intraventricular conduction disturbances, resting ST-segment and T-wave abnormalities, ventricular hypertrophy, or abnormal serum potassium levels. Obstructive disease limited to the circumflex coronary artery may result in a false-negative stress test since the posterolateral portion of the heart that this vessel supplies is not well represented on the surface 12-lead ECG. Since the overall sensitivity of an exercise stress ECG is only $\sim 75\%$, a negative result does not exclude CAD, although it makes the likelihood of three-vessel or left main CAD extremely unlikely.

A medical professional should be present throughout the exercise test. It is important to measure total duration of exercise, the times to the onset of ischemic ST-segment change and chest discomfort, the external work performed (generally expressed as the stage of exercise), and the internal cardiac work performed, i.e., by the heart rate–blood pressure product. The depth of the ST-segment depression and the time needed for recovery of these ECG changes are also important. Because the risks of exercise testing are small but real—estimated at one fatality and two nonfatal complications per 10,000 tests—equipment for resuscitation should be available. Modified (heart rate–limited rather than symptom–limited) exercise tests can be performed safely in patients as early as 6 days after uncomplicated myocardial infarction (Table 284-2). Contraindications to exercise stress testing include rest angina within 48 h, unstable rhythm, severe aortic stenosis, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

The normal response to graded exercise includes progressive increases in heart rate and blood pressure. Failure of the blood pressure to increase or an actual decrease with signs of ischemia during the test is an important adverse prognostic sign, since it may reflect ischemia-induced global LV dysfunction. The development of angina and/or severe (>0.2 mV) ST-segment depression at a low workload, i.e., before completion of stage II of the Bruce protocol, and/or ST-segment depression that persists >5 min after the termination of exercise increases the specificity of the test and suggests severe IHD and a high risk of future adverse events.

Cardiac Imaging (See also Chap. 248) When the resting ECG is abnormal (e.g., preexcitation syndrome, >1 mm of resting ST-segment depression, left bundle branch block, paced ventricular rhythm), information gained from an exercise test can be enhanced by stress myocardial radionuclide perfusion imaging after the intravenous administration of thallium-201 or 99m-technetium sestamibi during exercise (or with pharmacologic) stress. Contemporary data also suggest positron emission tomography (PET) imaging (with exercise or pharmacologic stress) using N-13 ammonia or rubidium-82 as another technique for assessing perfusion. Images obtained immediately after cessation of exercise to detect regional ischemia are compared with those obtained at rest to confirm reversible ischemia and regions of persistently absent uptake that signify infarction.

A sizable fraction of patients who need noninvasive stress testing to identify myocardial ischemia and increased risk of coronary events cannot exercise because of peripheral vascular or musculoskeletal disease, exertional dyspnea, or deconditioning. In these circumstances, an intravenous pharmacologic challenge is used in place of exercise. For example, adenosine can be given to create a coronary “steal” by temporarily increasing flow in nondiseased segments of the coronary vasculature at the expense of diseased segments. Alternatively, a graded incremental infusion of dobutamine may be administered to increase MVO₂. A variety of imaging options are available to accompany these pharmacologic stressors (Fig. 284-3). The development of a transient perfusion defect with a tracer such as thallium-201 or 99m-technetium sestamibi is used to detect myocardial ischemia.

Echocardiography is used to assess LV function in patients with chronic stable angina and patients with a history of a prior myocardial infarction, pathologic Q waves, or clinical evidence of heart failure. Two-dimensional echocardiography can assess both global and regional wall motion abnormalities of the left ventricle that are transient when due to ischemia. Stress (exercise or dobutamine) echocardiography may cause the emergence of regions of akinesis or dyskinesis that are not present at rest. Stress echocardiography, like stress myocardial perfusion imaging, is more sensitive than exercise electrocardiography

in the diagnosis of IHD. Cardiac magnetic resonance (CMR) stress testing is also evolving as an alternative to radionuclide, PET, or echocardiographic stress imaging. CMR stress testing performed with dobutamine infusion can be used to assess wall motion abnormalities accompanying ischemia, as well as myocardial perfusion. CMR can be used to provide more complete ventricular evaluation using multislice magnetic resonance imaging (MRI) studies.

Atherosclerotic plaques become progressively calcified over time, and coronary calcification in general increases with age. For this

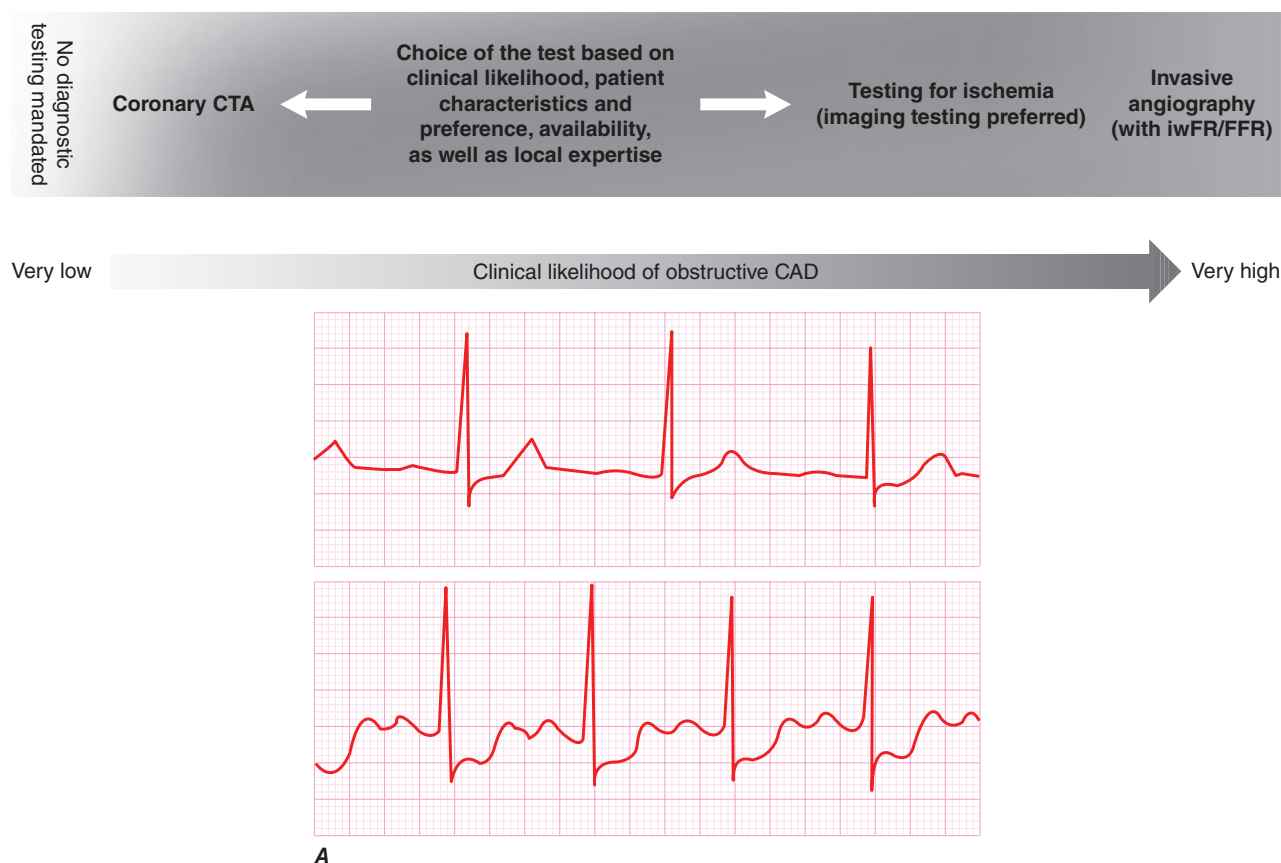


FIGURE 284-3 Selecting appropriate testing patients with angina and suspected coronary artery disease (CAD). On the left of the figure is an algorithm for selecting from among testing options. In patients who are at low risk, in whom prior testing was equivocal, or in whom the diagnosis of is CAD uncertain, noninvasive functional stress testing with imaging for myocardial ischemia or computed tomography angiography (CTA) is reasonable to establish the diagnosis of CAD prior to initiation of treatment. Patients with a high clinical likelihood of CAD, patients with symptoms despite antianginal therapy or with low-level activities, and patients with high-risk features based on the initial clinical evaluation may proceed directly to invasive coronary angiography without further diagnostic testing. (Adapted from J Knuuti et al: 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 41:407, 2020.) Panels A–F are examples of the data obtained with electrocardiogram (ECG) monitoring and specialized imaging procedures. CMR, cardiac magnetic resonance; EBCT, electron beam computed tomography; ECHO, echocardiography; FFR, fractional flow reserve; IHD, ischemic heart disease; iwFR, instantaneous wave-free ratio; MIBI, methoxyisobutyl isonitrite; MR, magnetic resonance; PET, positron emission tomography. **A.** Lead V₄ at rest (top panel) and after 4.5 min of exercise (bottom panel). There is 3 mm (0.3 mV) of horizontal ST-segment depression, indicating a positive test for ischemia. (Adapted from BR Chaitman, in E Braunwald et al [eds]: *Heart Disease*, 8th ed, Philadelphia, Saunders, 2008.) **B.** A 45-year-old avid jogger who began experiencing classic substernal chest pressure underwent an exercise echo study. With exercise, the patient's heart rate increased from 52 to 153 beats/min. The left ventricular chamber dilated with exercise, and the septal and apical portions became akinetic to dyskinetic (red arrow). These findings are strongly suggestive of a significant flow-limiting stenosis in the proximal left anterior descending artery, which was confirmed at coronary angiography. (Modified from SD Solomon, in E Braunwald et al [eds]: *Primary Cardiology*, 2nd ed, Philadelphia, Saunders, 2003.) **C.** Stress and rest myocardial perfusion single-photon emission computed tomography images obtained with 99m-technetium sestamibi in a patient with chest pain and dyspnea on exertion. The images demonstrate a medium-size and severe stress perfusion defect involving the inferolateral and basal inferior walls, showing nearly complete reversibility, consistent with moderate ischemia in the right coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.) **D.** A patient with a prior myocardial infarction presented with recurrent chest discomfort. On cardiac magnetic resonance (CMR) cine imaging, a large area of anterior akinesia was noted (marked by the arrows in the top left and right images, systolic frame only). This area of akinesia was matched by a larger extent of late gadolinium-DTPA enhancements consistent with a large transmural myocardial infarction (marked by arrows in the middle left and right images). Resting (bottom left) and adenosine vasodilating stress (bottom right) first-pass perfusion images revealed reversible perfusion abnormality that extended to the inferior septum. This patient was found to have an occluded proximal left anterior descending coronary artery with extensive collateral formation. This case illustrates the utility of different modalities in a CMR examination in characterizing ischemic and infarcted myocardium. DTPA, diethylenetriamine penta-acetic acid. (Images provided by Dr. Raymond Kwong, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.) **E.** Stress and rest myocardial perfusion PET images obtained with rubidium-82 in a patient with chest pain on exertion. The images demonstrate a large and severe stress perfusion defect involving the mid and apical anterior, anterolateral, and anteroapical walls and the left ventricular apex, showing complete reversibility, consistent with extensive and severe ischemia in the mid-left anterior descending coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.) **F.** A 58-year-old woman with psoriasis presented with chest discomfort and underwent coronary CT angiography (CCTA) for further evaluation. There was a large amount of mostly noncalcified plaque resulting in severe (>70%) stenosis of the mid left anterior descending artery (LAD) and the mid-right coronary artery (RCA). There was minimal plaque in the left circumflex (LCx). CCTA data can be used to reconstruct three-dimensional images to aid visualization. In addition, each coronary artery can be visualized en face by creating a short axis along the length of the coronary segment being visualized. In this case, the stenosis of the LAD is seen in the red box (corresponding to the level of the dashed red line) and compared with the proximal normal segment in the green box (corresponding to the level of the dashed green line). (Images provided by Dr. Ron Blankstein, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.)

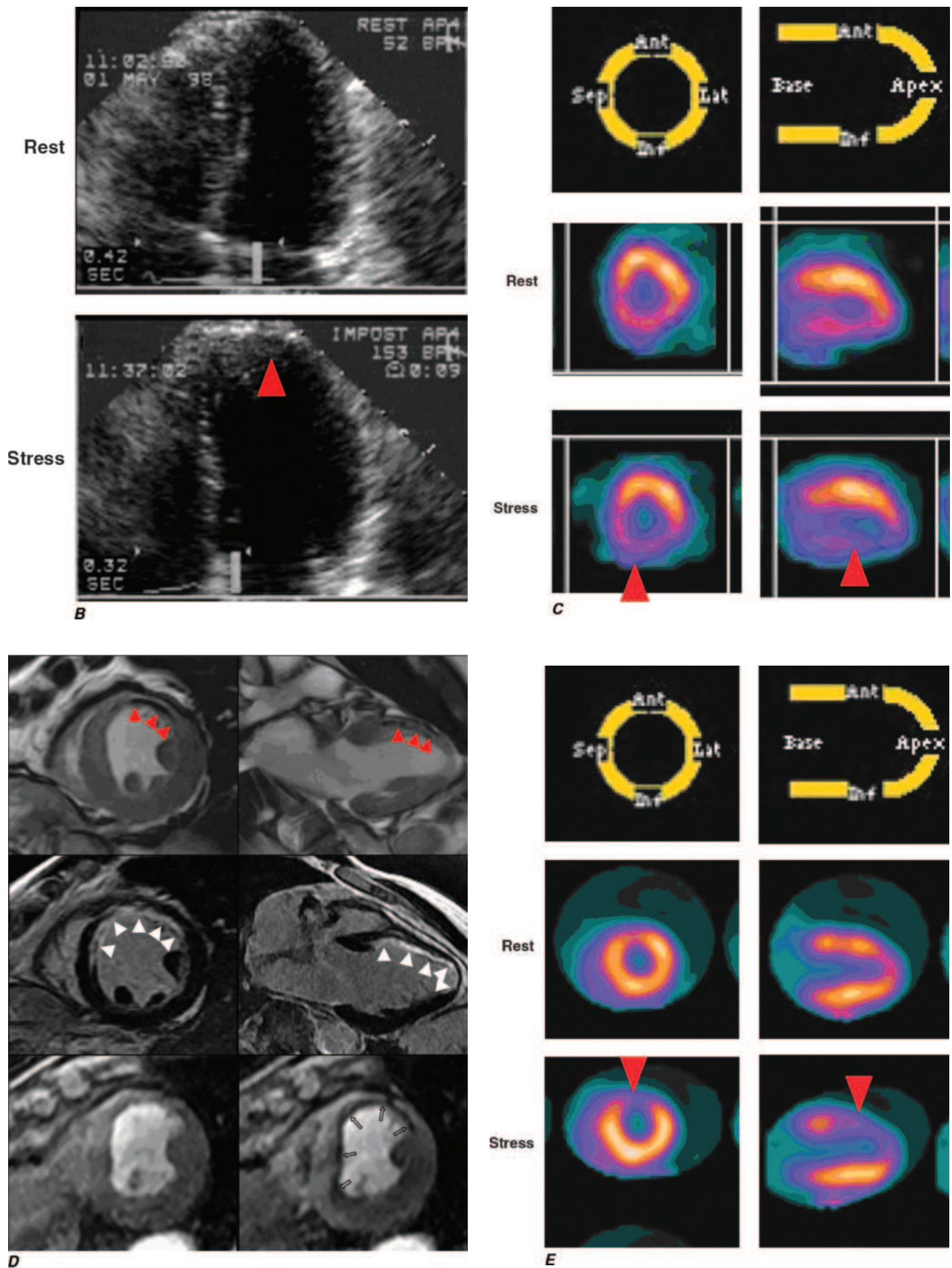


FIGURE 284-3 (Continued)

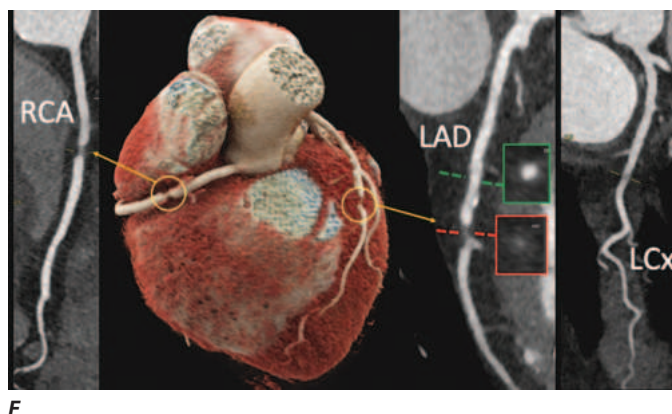


FIGURE 284-3 (Continued)

reason, methods for detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis. These methods involve CT applications that achieve rapid acquisition of images (electron beam [EBCT] and multidetector [MDCT] detection). Coronary calcium detected by these imaging techniques most commonly is quantified by using the Agatston score, which is based on the area and density of calcification.

Coronary CT angiography (CCTA) (Fig. 284-3) is helpful in diagnosing the extent and severity of nonobstructive and obstructive IHD, as well as assessing plaque composition. Thus, CCTA is an attractive option when the pretest likelihood of IHD is intermediate in a young patient (< 65 years) with chest pain or less obstructive IHD is suspected. Stress imaging is the preferred diagnostic test when the goal is assessing the adequacy of ischemia-guided management.

CORONARY ARTERIOGRAPHY

(See also Chap. 249) This diagnostic method outlines the lumina of the coronary arteries and can be used to detect or exclude serious coronary obstruction. However, coronary arteriography provides no

information about the arterial wall, and severe atherosclerosis that does not encroach on the lumen may go undetected. Of note, atherosclerotic plaques characteristically are scattered throughout the coronary tree, tend to occur more frequently at branch points, and grow progressively in the intima and media of an epicardial coronary artery at first without encroaching on the lumen, causing an outward bulging of the artery—a process referred to as remodeling. Later in the course of the disease, further growth causes luminal narrowing.

Indications The ISCHEMIA trial informs decision-making about referral for coronary arteriography (with intent to perform revascularization) in patients with stable IHD and an ejection fraction >35% even in the presence of moderate-severe ischemia on noninvasive functional testing. Over the course of 4 years of follow-up, early referral for an invasive strategy was not associated with a reduction in the risk of myocardial infarction or death but was more effective than an initial conservative, medical strategy in relieving angina. Thus, coronary arteriography is indicated in (1) patients with chronic stable angina pectoris who are severely symptomatic despite medical therapy and are

TABLE 284-2 Relation of Metabolic Equivalent Tasks (METs) to Stages in Various Testing Protocols

FUNCTIONAL CLASS	CLINICAL STATUS				O ₂ COST mL/Kg/min	METs	TREADMILL PROTOCOLS			
NORMAL AND I	HEALTHY, DEPENDENT ON AGE, ACTIVITY						BRUCE Modified 3 min Stages		BRUCE 3 min Stages	
							MPH	%GR	MPH	%GR
							6.0	22	6.0	22
							5.5	20	5.2	20
							5.0	18	5.0	18
					56.0	16				
					52.5	15				
					49.0	14				
					45.5	13	4.2	16	4.2	16
					42.0	12				
	38.5	11	3.4	14	3.4	14				
	35.0	10								
	31.5	9								
	28.0	8								
24.5	7	2.5	12	2.5	12					
II				SYMPTOMATIC	21.0	6				
17.5					5	1.7	10	1.7	10	
14.0					4					
10.5					3	1.7	5			
7.0					2	1.7	0			
IV								3.5	1	

Note: The standard Bruce treadmill protocol (right-hand column) begins at 1.7 MPH and 10% gradient (GR) and progresses every 3 min to a higher speed and elevation. The corresponding oxygen consumption and clinical status of the patient are shown in the center and left-hand columns.

Abbreviations: GR, grade; MPH, miles per hour.

Source: Reproduced with permission from GF Fletcher et al: Exercise standards for testing and training. *Circulation* 104:1694, 2001.

being considered for revascularization, i.e., a percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); (2) patients with troublesome symptoms that present diagnostic difficulties in whom there is a need to confirm or rule out the diagnosis of IHD; (3) patients with known or possible angina pectoris who have survived cardiac arrest; and (4) patients with angina or evidence of ischemia on noninvasive testing with clinical or laboratory evidence of ventricular dysfunction.

Examples of other indications for coronary arteriography include the following:

1. Patients with chest discomfort suggestive of angina pectoris but a negative or nondiagnostic stress test who require a definitive diagnosis for guiding medical management, alleviating psychological stress, career or family planning, or insurance purposes.
2. Patients who have been admitted repeatedly to the hospital for a suspected acute coronary syndrome (**Chaps. 285 and 286**), but in whom this diagnosis has not been established and in whom it is considered clinically important to determine the presence or absence of CAD.
3. Patients with careers that involve the safety of others (e.g., pilots, firefighters, police) who have questionable symptoms or suspicious or positive noninvasive tests and in whom there are reasonable doubts about the state of the coronary arteries.
4. Patients with aortic stenosis or hypertrophic cardiomyopathy and angina in whom the chest pain could be due to IHD.
5. Male patients >45 years and females >55 years who are to undergo a cardiac operation such as valve replacement or repair and who may or may not have clinical evidence of myocardial ischemia.
6. Patients after myocardial infarction, especially those who are at high risk after myocardial infarction because of the recurrence of angina or the presence of heart failure, frequent ventricular premature contractions, or signs of ischemia on the stress test.
7. Patients in whom coronary spasm or another nonatherosclerotic cause of myocardial ischemia (e.g., coronary artery anomaly, Kawasaki disease) is suspected.

Noninvasive alternatives to diagnostic coronary arteriography include CT angiography and CMR angiography (**Chap. 248**). Important aspects of their use that should be noted include the substantially higher radiation exposure with CT angiography compared to conventional diagnostic arteriography and the limitations on CMR imposed by cardiac movement during the cardiac cycle, especially at high heart rates.

■ PROGNOSIS

The principal prognostic indicators in patients known to have IHD are age, the functional state of the left ventricle, the location(s) and severity of coronary artery narrowing, and the severity or activity of myocardial ischemia. Angina pectoris of recent onset, unstable angina (**Chap. 285**), early postmyocardial infarction angina, angina that is unresponsive or poorly responsive to medical therapy, and angina accompanied by symptoms of congestive heart failure all indicate an increased risk for adverse coronary events. The same is true for the physical signs of heart failure, episodes of pulmonary edema, transient third heart sounds, and mitral regurgitation and for echocardiographic or radioisotopic (or roentgenographic) evidence of cardiac enlargement and reduced (<0.40) ejection fraction.

Most important, any of the following signs during noninvasive testing indicates a high risk for coronary events: inability to exercise for 6 min, i.e., stage II (Bruce protocol) of the exercise test; a strongly positive exercise test showing onset of myocardial ischemia at low workloads (≥ 0.1 mV ST-segment depression before completion of stage II, ≥ 0.2 mV ST-segment depression at any stage, ST-segment depression for >5 min after the cessation of exercise, a decline in systolic pressure >10 mmHg during exercise, or the development of ventricular tachyarrhythmias during exercise); the development of large or multiple perfusion defects or increased lung uptake during stress radioisotope perfusion imaging; and a decrease in LV ejection fraction during exercise on radionuclide ventriculography or during stress echocardiography. Conversely, patients who can complete stage III of the Bruce

exercise protocol and have a normal stress perfusion scan or negative stress echocardiographic evaluation are at very low risk for future coronary events. The finding of frequent episodes of ST-segment deviation on ambulatory ECG monitoring (even in the absence of symptoms) is also an adverse prognostic finding.

On cardiac catheterization, elevations of LV end-diastolic pressure and ventricular volume and reduced ejection fraction are the most important signs of LV dysfunction and are associated with a poor prognosis. Patients with chest discomfort but normal LV function and normal coronary arteries have an excellent prognosis. Obstructive lesions of the left main (>50% luminal diameter) or left anterior descending coronary artery proximal to the origin of the first septal artery are associated with a greater risk than are lesions of the right or left circumflex coronary artery because of the greater quantity of myocardium at risk. Atherosclerotic plaques in epicardial arteries with fissuring or filling defects indicate increased risk. These lesions go through phases of inflammatory cellular activity, degeneration, endothelial dysfunction, abnormal vasomotion, platelet aggregation, and fissuring or hemorrhage. These factors can temporarily worsen the stenosis and cause thrombosis and/or abnormal reactivity of the vessel wall, thus exacerbating the manifestations of ischemia. The recent onset of symptoms, the development of severe ischemia during stress testing (see above), and unstable angina pectoris (**Chap. 285**) all reflect episodes of rapid progression in coronary lesions.

With any degree of obstructive CAD, mortality is greatly increased when LV function is impaired; conversely, at any level of LV function, the prognosis is influenced importantly by the quantity of myocardium perfused by critically obstructed vessels. Therefore, it is essential to collect all the evidence substantiating past myocardial damage (evidence of myocardial infarction on ECG, echocardiography, radioisotope imaging, or left ventriculography), residual LV function (ejection fraction and wall motion), and risk of future damage from coronary events (extent of coronary disease and severity of ischemia defined by noninvasive stress testing). The larger the quantity of established myocardial necrosis is, the less the heart is able to withstand additional damage and the poorer the prognosis. Risk estimation must include age, presenting symptoms, all risk factors, signs of arterial disease, existing cardiac damage, and signs of impending damage (i.e., ischemia).

The greater the number and severity of risk factors for coronary atherosclerosis (advanced age >75 years], hypertension, dyslipidemia, diabetes, morbid obesity, accompanying peripheral and/or cerebrovascular disease, previous myocardial infarction), the worse the prognosis of an angina patient. Evidence exists that elevated levels of CRP in the plasma, extensive coronary calcification on EBCT (see above), and increased carotid intimal thickening on ultrasound examination also indicate an increased risk of coronary events.

TREATMENT

Stable Angina Pectoris

Once the diagnosis of IHD has been made, each patient must be evaluated individually with respect to their level of understanding, expectations and goals, control of symptoms, and prevention of adverse clinical outcomes such as myocardial infarction and premature death. The degree of disability and the physical and emotional stress that precipitates angina must be recorded carefully to set treatment goals. The management plan should include the following components: (1) explanation of the problem and reassurance about the ability to formulate a treatment plan, (2) identification and treatment of aggravating conditions, (3) recommendations for adaptation of activity as needed, (4) treatment of risk factors that will decrease the occurrence of adverse coronary outcomes, (5) drug therapy for angina, and (6) consideration of revascularization. Emphasis should be placed on a patient-centric, team-based approach to care, with recognition of the importance of social determinants of health.

EXPLANATION AND REASSURANCE

Patients with IHD need to understand their condition and realize that a long and productive life is possible even though they have angina pectoris or have experienced and recovered from an acute

myocardial infarction. Offering results of clinical trials showing improved outcomes can be of great value in encouraging patients to resume or maintain activity and return to work. A planned program of rehabilitation can encourage patients to lose weight, improve exercise tolerance, and control risk factors with more confidence.

IDENTIFICATION AND TREATMENT OF AGGRAVATING CONDITIONS

A number of conditions may increase oxygen demand or decrease oxygen supply to the myocardium and may precipitate or exacerbate angina in patients with IHD. LVH, aortic valve disease, and hypertrophic cardiomyopathy may cause or contribute to angina and should be excluded or treated. Obesity, hypertension, and hyperthyroidism should be treated aggressively to reduce the frequency and severity of anginal episodes. Decreased myocardial oxygen supply may be due to reduced oxygenation of the arterial blood (e.g., in pulmonary disease or, when carboxyhemoglobin is present, due to cigarette or cigar smoking) or decreased oxygen-carrying capacity (e.g., in anemia). Correction of these abnormalities, if present, may reduce or even eliminate angina pectoris.

ADAPTATION OF ACTIVITY

Myocardial ischemia is caused by a discrepancy between the demand of the heart muscle for oxygen and the ability of the coronary circulation to meet that demand. Most patients can be helped to understand this concept and utilize it in the rational programming of activity. Many tasks that ordinarily evoke angina may be accomplished without symptoms simply by reducing the speed at which they are performed. Patients must appreciate the diurnal variation in their tolerance of certain activities and reducing their energy requirements in the morning, immediately after meals, and in cold or inclement weather. On occasion, it may be necessary to recommend a change in employment or residence to avoid physical stress.

Physical conditioning usually improves the exercise tolerance of patients with angina and has substantial psychological benefits. A regular program of isotonic exercise that is within the limits of

the individual patient's threshold for the development of angina pectoris and that does not exceed 80% of the heart rate associated with ischemia on exercise testing should be strongly encouraged. Based on the results of an exercise test, the number of metabolic equivalent tasks (METs) performed at the onset of ischemia can be estimated (Table 284-2) and a practical exercise prescription can be formulated to permit daily activities that will fall below the ischemic threshold (Table 284-3).

TREATMENT OF RISK FACTORS

A *family history* of premature IHD is an important indicator of increased risk and should trigger a search for treatable risk factors such as hyperlipidemia, hypertension, and diabetes mellitus. *Obesity* impairs the treatment of other risk factors and increases the risk of adverse coronary events. In addition, obesity often is accompanied by three other risk factors: diabetes mellitus, hypertension, and hyperlipidemia. The treatment of obesity and these accompanying risk factors is an important component of any management plan. A diet low in saturated and *trans*-unsaturated fatty acids and a reduced caloric intake to achieve optimal body weight are a cornerstone in the management of chronic IHD. It is especially important to emphasize weight loss and regular exercise in patients with the metabolic syndrome or overt diabetes mellitus.

Cigarette smoking accelerates coronary atherosclerosis in both sexes and at all ages and increases the risk of thrombosis, plaque instability, myocardial infarction, and death. In addition, by increasing myocardial oxygen needs and reducing oxygen supply, it aggravates angina. Smoking cessation studies have demonstrated important benefits with a significant decline in the occurrence of these adverse outcomes. Noncombustible tobacco in the form of electronic cigarettes (nicotine delivery systems) may also increase the frequency of anginal episodes. The physician's message must be clear and strong and supported by programs that achieve and monitor abstinence from all tobacco product use (Chap. 465).

TABLE 284-3 Energy Requirements for Some Common Activities

LESS THAN 3 METs	3-5 METs	5-7 METs	7-9 METs	MORE THAN 9 METs
Self-Care				
Washing/shaving	Cleaning windows	Easy digging in garden	Heavy shoveling	Carrying loads upstairs (objects >90 lb)
Dressing	Raking	Level hand lawn mowing	Carrying objects (60-90 lb)	Climbing stairs (quickly)
Light housekeeping	Power lawn mowing	Carrying objects (30-60 lb)		Shoveling heavy snow
Desk work	Bed making/stripping			
Driving auto	Carrying objects (15-30 lb)			
Occupational				
Sitting (clerical/assembly)	Stocking shelves (light objects)	Carpentry (exterior)	Digging ditches (pick and shovel)	Heavy labor
Desk work	Light welding/carpentry	Shoveling dirt		
Standing (store clerk)		Sawing wood		
Recreational				
Golf (cart)	Dancing (social)	Tennis (singles)	Canoeing	Squash
Knitting	Golf (walking)	Snow skiing (downhill)	Mountain climbing	Ski touring
	Sailing	Light backpacking		Vigorous basketball
	Tennis (doubles)	Basketball		
		Stream fishing		
Physical Conditioning				
Walking (2 mph)	Level walking (3-4 mph)	Level walking (4.5-5.0 mph)	Level jogging (5 mph)	Running more than 6 mph
Stationary bike	Level biking (6-8 mph)	Bicycling (9-10 mph)	Swimming (crawl stroke)	Bicycling (more than 13 mph)
Very light calisthenics	Light calisthenics	Swimming, breast stroke	Rowing machine	Rope jumping
			Heavy calisthenics	Walking uphill (5 mph)
			Bicycling (12 mph)	

Abbreviation: METs, metabolic equivalent tasks.

Source: Modified from WL Haskell: Rehabilitation of the coronary patient, in NK Wenger, HK Hellerstein (eds): *Design and Implementation of Cardiac Conditioning Program*. New York, Churchill Livingstone, 1978.

Hypertension (Chap. 288) may coexist with other risk factors for IHD and is associated with an increased risk of adverse clinical events from coronary atherosclerosis as well as stroke. In addition, the LVH that results from sustained hypertension aggravates ischemia. There is evidence that long-term effective treatment of hypertension can decrease the occurrence of adverse coronary events (**Chap. 288**).

Diabetes mellitus (Chap. 415) accelerates coronary, cerebrovascular, and peripheral atherosclerosis and is frequently associated with dyslipidemia and increases in the risk of angina, myocardial infarction, and sudden coronary death. Aggressive control of the dyslipidemia (target LDL cholesterol <70 mg/dL) and hypertension (blood pressure <130/80 mmHg), that are frequently found in patients with diabetes mellitus, is highly effective and therefore essential, as described below. Use of either a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist in patients with IHD and type 2 diabetes is recommended in current guidelines to reduce the risk of major adverse cardiovascular events.

DYSLIPIDEMIA

The treatment of dyslipidemia is central in aiming for long-term relief from angina, reduced need for revascularization, and reduction in myocardial infarction and death. The control of lipids can be achieved by the combination of a diet low in saturated and *trans*-unsaturated fatty acids, exercise, and weight loss. Nearly always, HMG-CoA reductase inhibitors (statins) are required and can lower LDL cholesterol (25–50%), raise HDL cholesterol (5–9%), and lower triglycerides (5–30%). A powerful treatment effect of statins on atherosclerosis, IHD, and outcomes is seen regardless of the pretreatment LDL cholesterol level. In patients with IHD on a maximally tolerated statin with an LDL cholesterol ≥70 mg/dL, addition of ezetimibe is recommended as the next step, followed by a PCSK9 inhibitor (in patients at very high risk) should the LDL cholesterol goal not be achieved. When these therapies are not sufficient or tolerated, bempedoic acid may be considered for further LDL cholesterol reduction. Icosapent ethyl (purified eicosapentaenoic acid), fibrates, and resin-binding agents can be used to lower triglycerides (**Chap. 419**), but only icosapent ethyl has been shown to reduce cardiovascular risk in the statin era. Controlled trials with lipid-regulating regimens have shown equal proportional benefit for men, women, the elderly, patients with diabetes mellitus, and smokers. Evidence exists that a high rate of control of LDL over time is associated with a lower cumulative LDL exposure and lower rate of major adverse cardiovascular events.

Compliance with the health-promoting behaviors listed above is generally very poor, and a conscientious physician must not underestimate the major effort required to meet this challenge. Many patients who are discharged from the hospital with proven coronary disease do not receive adequate treatment for dyslipidemia. In light of the proof that treating dyslipidemia brings major benefits, physicians need to establish treatment pathways, monitor compliance, and follow up regularly.

RISK REDUCTION IN WOMEN WITH IHD

The incidence of clinical IHD in premenopausal women is very low; however, after menopause, the atherogenic risk factors increase (e.g., increased LDL) and the rate of clinical coronary events accelerates to the levels observed in men. Diabetes mellitus, which is more common in women, greatly increases the occurrence of clinical IHD and amplifies the deleterious effects of hypertension, hyperlipidemia, and smoking. Cardiac catheterization and coronary revascularization are underused in women and are performed at a later and more severe stage of the disease than in men. When cholesterol lowering, beta blockers after myocardial infarction, and CABG are applied in the appropriate patient groups, women benefit to the same degree as men.

DRUG THERAPY

The commonly used drugs for the treatment of angina pectoris are summarized in **Tables 284-4 through 284-6**. Pharmacotherapy for IHD is designed to reduce the frequency of anginal episodes,

TABLE 284-4 Nitrate Therapy in Patients with Ischemic Heart Disease

PREPARATION OF AGENT	DOSE	SCHEDULE
Nitroglycerin ^a	Ointment	0.5–2 in.
	Transdermal patch	0.2–0.8 mg/h
	Sublingual tablet	0.3–0.6 mg
	Spray	One or two sprays
Isosorbide dinitrate ^a	Oral	10–40 mg
	Oral sustained release	80–120 mg
	Isosorbide 5-mononitrate	20 mg
Oral sustained release	30–240 mg	Once daily

^aA 10- to 12-h nitrate-free interval is recommended.
Source: Reproduced with permission from DA Morrow, WE Boden: Stable ischemic heart disease. In RO Bonow et al (eds): *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 9th ed. Philadelphia, Saunders, 2012.

myocardial infarction, and coronary death. Trial data emphasize how important medical management is when added to the health-promoting behaviors discussed above. To achieve maximum benefit from medical therapy for IHD, it is frequently necessary to combine agents from different classes and titrate the doses as guided by the individual profile of risk factors, symptoms, hemodynamic responses, and side effects.

NITRATES

The organic nitrates are a valuable class of drugs in the management of angina pectoris (Table 284-4). Their major mechanisms of action include systemic venodilation with concomitant reduction in LV end-diastolic volume and pressure, thereby reducing myocardial wall tension and oxygen requirements; dilation of epicardial coronary vessels; and increased blood flow in collateral vessels. When metabolized, organic nitrates release nitric oxide (NO) that binds to guanylyl cyclase in vascular smooth muscle

TABLE 284-5 Properties of Beta Blockers in Clinical Use for Ischemic Heart Disease

DRUGS	SELECTIVITY	PARTIAL AGONIST ACTIVITY	USUAL DOSE FOR ANGINA
Acebutolol	β ₁	Yes	200–600 mg twice daily
Atenolol	β ₁	No	50–200 mg/d
Betaxolol	β ₁	No	10–20 mg/d
Bisoprolol	β ₁	No	10 mg/d
Esmolol (intravenous) ^a	β ₁	No	50–300 µg/kg/min
Labetalol ^b	None	Yes	200–600 mg twice daily
Metoprolol	β ₁	No	50–200 mg twice daily
Nadolol	None	No	40–80 mg/d
Nebivolol	β ₁ (at low doses)	No	5–40 mg/d
Pindolol	None	Yes	2.5–7.5 mg 3 times daily
Propranolol	None	No	80–120 mg twice daily
Timolol	None	No	10 mg twice daily

^aEsmolol is an ultra-short-acting beta blocker that is administered as a continuous intravenous infusion. Its rapid offset of action makes esmolol an attractive agent to use in patients with relative contraindications to beta blockade. ^bLabetalol is a combined alpha and beta blocker.
Note: This list of beta blockers that may be used to treat patients with angina pectoris is arranged alphabetically. It is preferable to use a sustained-release formulation that may be taken once daily to improve the patient's compliance with the regimen.
Source: Data from RJ Gibbons et al: *J Am Coll Cardiol* 41:159, 2003.

TABLE 284-6 Calcium Channel Blockers in Clinical Use for Ischemic Heart Disease

DRUGS	USUAL DOSE	DURATION OF ACTION	SIDE EFFECTS
Dihydropyridines			
Amlodipine	5–10 mg qd	Long	Headache, edema
Felodipine	5–10 mg qd	Long	Headache, edema
Isradipine	2.5–10 mg bid	Medium	Headache, fatigue
Nicardipine	20–40 mg tid	Short	Headache, dizziness, flushing, edema
Nifedipine	Immediate release: ^a 30–90 mg daily orally Slow release: 30–180 mg orally	Short	Hypotension, dizziness, flushing, nausea, constipation, edema
Nisoldipine	20–40 mg qd	Short	Similar to nifedipine
Nondihydropyridines			
Diltiazem	Immediate release: 30–80 mg 4 times daily	Short	Hypotension, dizziness, flushing, bradycardia, edema
	Slow release: 120–320 mg qd	Long	
Verapamil	Immediate release: 80–160 mg tid	Short	Hypotension, myocardial depression, heart failure, edema, bradycardia
	Slow release: 120–480 mg qd	Long	

^aMay be associated with increased risk of mortality if administered during acute myocardial infarction.

Note: This list of calcium channel blockers that may be used to treat patients with angina pectoris is divided into two broad classes, dihydropyridines and nondihydropyridines, and arranged alphabetically within each class. Among the dihydropyridines, the greatest clinical experience has been obtained with amlodipine and nifedipine. After the initial period of dose titration with a short-acting formulation, it is preferable to switch to a sustained-release formulation that may be taken once daily to improve patient compliance with the regimen.

Source: Data from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

cells, leading to an increase in cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle. Nitrates also exert antithrombotic activity by NO-dependent activation of platelet guanylyl cyclase, impairment of intraplatelet calcium flux, and platelet activation.

The absorption of these agents is rapid and complete through mucous membranes. For this reason, nitroglycerin is most commonly administered sublingually in tablets of 0.4 or 0.6 mg. Patients with angina should be instructed to take the medication both to relieve angina and also ~5 min before activities that are likely to induce an episode.

Nitrates improve exercise tolerance in patients with chronic angina and relieve ischemia in patients with unstable angina as well as patients with vasospastic variant angina (**Chap. 285**). A diary of angina and nitroglycerin use may be valuable for detecting changes in the frequency, severity, or threshold for discomfort that may signify the development of unstable angina pectoris and/or herald an impending myocardial infarction.

Long-Acting Nitrates None of the long-acting nitrates is as effective as sublingual nitroglycerin for the acute relief of angina. These organic nitrate preparations can be swallowed, chewed, or administered as a patch or paste by the transdermal route (Table 284-4). They provide effective plasma levels for up to 24 h, but the therapeutic response is highly variable. Different preparations and/or administration during the daytime should be tried only to prevent discomfort while avoiding side effects such as headache and dizziness. Individual dose titration is important to prevent side effects. To minimize the effects of nitrate tolerance, the minimum effective dose should be used and a minimum of 8 h each day kept free of the drug to restore any useful response(s).

Beta-Adrenergic Blockers These drugs represent an important component of the pharmacologic treatment of angina pectoris (Table 284-5). They reduce myocardial oxygen demand by inhibiting the increases in heart rate, arterial pressure, and myocardial contractility caused by adrenergic activation. Beta blockade reduces these variables most strikingly during exercise but causes only small reductions at rest. Long-acting beta-blocking drugs or sustained-release formulations offer the advantage of once-daily dosing (Table 284-5). The therapeutic aims include relief of angina and ischemia. These drugs also can reduce mortality and reinfarction rates in patients after myocardial infarction and are moderately effective antihypertensive agents. Use of beta blockers beyond 1 year after myocardial infarction may be reassessed in the absence of LV systolic dysfunction, angina, arrhythmias, or uncontrolled hypertension, as their long-term benefit in such patients is unclear.

Relative contraindications include asthma and reversible airway obstruction in patients with chronic lung disease, atrioventricular conduction disturbances, severe bradycardia, Raynaud's phenomenon, and a history of mental depression. Side effects include fatigue, reduced exercise tolerance, nightmares, impotence, cold extremities, intermittent claudication, bradycardia (sometimes severe), impaired atrioventricular conduction, LV failure, bronchial asthma, worsening claudication, and intensification of the hypoglycemia produced by oral hypoglycemic agents and insulin. Reducing the dose or even discontinuation may be necessary if these side effects develop and persist. Since sudden discontinuation can intensify ischemia, the doses should be tapered over 2 weeks. Beta blockers with relative β_1 -receptor specificity such as metoprolol and atenolol may be preferable in patients with mild bronchial obstruction and insulin-requiring diabetes mellitus.

Calcium Channel Blockers Calcium channel blockers (Table 284-6) are coronary vasodilators that produce variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. These combined pharmacologic effects are advantageous and make these agents as effective as beta blockers in the treatment of angina pectoris. They are indicated when beta blockers are contraindicated, poorly tolerated, or ineffective. Because of differences in the dose-response relationship on cardiac electrical activity between the dihydropyridine and nondihydropyridine calcium channel blockers, verapamil and diltiazem may produce symptomatic disturbances in cardiac conduction and bradyarrhythmias. They also exert negative inotropic actions and are more likely to aggravate LV failure, particularly when used in patients with LV dysfunction, especially if the patients are also receiving beta blockers. Although useful effects usually are achieved when calcium channel blockers are combined with beta blockers and nitrates, individual titration of the doses is essential with these combinations. Vasospastic angina responds particularly well to calcium channel blockers (especially members of the dihydropyridine class), supplemented when necessary by nitrates (**Chap. 285**).

Verapamil ordinarily should not be combined with beta blockers because of the combined adverse effects on heart rate and contractility. Diltiazem can be combined with beta blockers in patients with normal ventricular function and no conduction disturbances. Amlodipine and beta blockers have complementary actions on coronary blood supply and myocardial oxygen demands. Whereas the former decreases blood pressure and dilates coronary arteries, the latter slows heart rate and decreases contractility. Amlodipine and the other second-generation dihydropyridine calcium antagonists (nicardipine, isradipine, long-acting nifedipine, and felodipine) are potent vasodilators and are useful in the simultaneous treatment of angina and hypertension. Short-acting dihydropyridines should be avoided because of the risk of precipitating infarction, particularly in the absence of concomitant beta blocker therapy.

Choice Between Beta Blockers and Calcium Channel Blockers for Initial Therapy Since beta blockers have been shown to improve life expectancy after acute myocardial infarction (**Chaps. 285 and 286**) and calcium channel blockers have not, the former may also be preferable in patients with angina and a damaged left ventricle. However, calcium channel blockers are indicated in patients with the following: (1) inadequate responsiveness to the combination of beta blockers and nitrates; many of these patients do well with a combination of a beta blocker and a dihydropyridine calcium channel blocker; (2) adverse reactions to beta blockers such as depression, sexual disturbances, and fatigue; (3) angina and a history of asthma or chronic obstructive pulmonary disease; (4) sick-sinus syndrome or significant atrioventricular conduction disturbances; (5) vasospastic angina; or (6) symptomatic peripheral arterial disease.

Ranolazine, a piperazine derivative, may be useful for patients with chronic angina despite standard medical therapy (**Table 284-7**). Its antianginal action is believed to occur via inhibition of the late inward sodium current (I_{Na}). The benefits of I_{Na} inhibition include limitation of the Na overload of ischemic myocytes and prevention of Ca^{2+} overload via the Na^+-Ca^{2+} exchanger. A dose of 500–1000 mg orally twice daily is usually well tolerated. Ranolazine is contraindicated in patients with hepatic impairment or with conditions or drugs associated with QT_c prolongation, and when drugs that inhibit the CYP3A metabolic system (e.g., ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and large quantities of grapefruit juice) are being used.

A comparison of the common side effects, contraindications, and potential drug interactions of many of the frequently presented antianginal agents is shown in Table 284-7.

Antiplatelet Drugs Aspirin is an irreversible inhibitor of platelet cyclooxygenase and thereby interferes with platelet activation. Chronic administration of 75–325 mg orally per day has been shown to reduce coronary events in asymptomatic adult men over age 50, patients with chronic stable angina, and patients who have or have survived unstable angina and myocardial infarction. There is a dose-dependent increase in bleeding when aspirin is used chronically. It is preferable to use an enteric-coated formulation in the range of 75–162 mg/d. Administration of this drug should be considered in all patients with IHD in the absence of gastrointestinal bleeding, allergy, or dyspepsia. Clopidogrel (300–600 mg

loading and 75 mg/d) is an oral agent that blocks $P2Y_{12}$ ADP receptor-mediated platelet aggregation. It provides benefits similar to those of aspirin in patients with stable chronic IHD and may be substituted for aspirin if aspirin causes the side effects listed above. Clopidogrel combined with aspirin reduces death and coronary ischemic events in patients with an acute coronary syndrome (**Chap. 285**) and also reduces the risk of thrombus formation in patients undergoing implantation of a stent in a coronary artery (**Chap. 287**). Alternative antiplatelet agents that block the $P2Y_{12}$ platelet receptor such as prasugrel and ticagrelor have been shown to be more effective than clopidogrel for prevention of ischemic events after placement of a stent for an acute coronary syndrome but are associated with an increased risk of bleeding. Although combined treatment with clopidogrel and aspirin for at least a year is recommended in patients with an acute coronary syndrome treated with implantation of a drug-eluting stent, studies have not shown any benefit from the routine addition of clopidogrel to aspirin in patients with chronic stable IHD.

OTHER THERAPIES

ACE inhibitors and ARBs are widely used in the treatment of survivors of myocardial infarction, patients with hypertension or chronic IHD including angina pectoris, and those at high risk of vascular diseases such as diabetes. The benefits of ACE inhibitors and ARBs are most evident in IHD patients at increased risk, especially if diabetes mellitus or LV dysfunction is present, and those who have not achieved adequate control of blood pressure and LDL cholesterol on beta blockers and statins. However, the routine administration of ACE inhibitors or ARBs to IHD patients who have normal LV function and have achieved blood pressure and LDL goals on other therapies does not reduce the incidence of events and therefore is not cost-effective.

Despite treatment with nitrates, beta blockers, calcium channel blockers, and ranolazine, some patients with IHD continue to experience angina, and additional medical therapy is now available to alleviate their symptoms.

Originally introduced for the management of diabetes mellitus, the SGLT-2 inhibitor drugs have emerged as important agents with cardiovascular and renal protective effects. They promote weight loss, lower blood pressure, and reduce plasma volume—all of which are desirable in patients with IHD. In addition, they decrease

TABLE 284-7 Antianginal Agents

AGENT	COMMON SIDE EFFECTS	CONTRAINDICATIONS	POTENTIAL DRUG INTERACTIONS
Agents That Have a Physiologic Effect			
<i>Short-acting and long-acting nitrates</i>	Headache, flushing, hypotension, syncope and postural hypotension, reflex tachycardia, methemoglobinemia	Hypertrophic obstructive cardiomyopathy	Phosphodiesterase type 5 inhibitors (sildenafil and similar agents), beta-adrenergic blockers, calcium channel blockers
<i>Beta blockers</i>	Fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, masked signs of hypoglycemia	Low heart rate or heart conduction disorder, cardiogenic shock, asthma, severe peripheral vascular disease, decompensated heart failure, vasospastic angina; use with caution in patients with COPD (cardioselective beta blockers may be used if patient receives adequate treatment with long-acting beta agonists)	Heart rate-lowering calcium channel blockers, sinus node or AV conduction depressors
<i>Calcium-channel blockers</i> Heart rate-lowering agents	Bradycardia, heart conduction defect, low ejection fraction, constipation, gingival hyperplasia	Cardiogenic shock, severe aortic stenosis, obstructive cardiomyopathy	CYP3A4 substrates (digoxin, simvastatin, cyclosporine)
Dihydropyridine	Headache, ankle swelling, fatigue, flushing, reflex tachycardia	Low heart rate or heart rhythm disorder, sick-sinus syndrome, congestive heart failure, low blood pressure	Agents with cardiodepressant effects (beta blockers, flecainide), CYP3A4 substrates
Agents That Affect Myocardial Metabolism			
Ranolazine	Dizziness, constipation, nausea, QT interval prolongation	Liver cirrhosis	CYP3A4 substrates (digoxin, simvastatin, cyclosporine), drugs that prolong the corrected QT interval

Abbreviations: AV, atrioventricular; COPD, chronic obstructive pulmonary disease; CYP3A4, cytochrome P450 3A4.

Source: Data from SE Husted: Lancet 386:691, 2015, and EM Ohman: N Engl J Med 374:1167, 2016.

intraglomerular hypertension and hyperfiltration. Evidence exists that they are helpful in patients with and without diabetes who have a reduced LV ejection fraction.

Colchicine exhibits a number of broad cellular effects (interferes with chemotaxis and phagocytosis of inflammatory cells, reduces the expression of adhesion molecules, modifies cytokine production) that result in an anti-inflammatory effect and may favorably affect the progression of atherosclerosis. In placebo-controlled randomized trials after myocardial infarction, low-dose colchicine (0.5 mg daily) prevented future cardiovascular events; however because it has a narrow therapeutic window, has a long half-life dependent upon renal clearance, is metabolized by CYP3A4, and is a substrate for P-glycoprotein (both of which may result in drug-drug interactions), additional monitoring is required.

In contrast, nonsteroidal anti-inflammatory drug (NSAID) use in patients with IHD may be associated with a small but finite increased risk of myocardial infarction and mortality. For this reason, they generally should be avoided in IHD patients. If they are required for symptom relief, it is advisable to coadminister aspirin and strive to use an NSAID associated with the lowest risk of cardiovascular events, in the lowest dose required, and for the shortest period of time.

Nicorandil opens ATP-sensitive potassium channels in myocytes, leading to a reduction of free intracellular calcium ions. It is typically administered orally in a dose of 20 mg twice daily for prevention of angina. Nicorandil is not available for use in the United States but is used in several other countries and is recommended as second-line treatment in the European chronic coronary disease (CCD) guidelines. Similarly, trimetazidine, which improves mitochondrial metabolism through inhibition of myocardial fatty acid uptake and oxidation and consequent stimulation of glucose oxidation, is recommended as a second-line antianginal in CCD and is available in many countries outside the United States.

Ivabradine (2.5–7.5 mg orally twice daily) is a specific sinus node inhibiting agent that may be helpful for preventing cardiovascular events in patients with IHD who have a resting heart rate ≥ 70 beats/min (alone or in combination with a beta blocker) and LV systolic dysfunction. However, the data are mixed regarding its clinical benefit, with the most recent U.S. CCD guideline recommending against its use in patients with normal LV function due to an increased risk of death or myocardial infarction).

Angina and Heart Failure Transient LV failure with angina can be controlled by the use of nitrates. For patients with established congestive heart failure, the increased LV wall tension raises myocardial oxygen demand. See [Chap. 265](#) for the “pillars” of treatment for heart failure. Treatment of congestive heart failure ([Chap. 264](#)) reduces heart size, wall tension, and myocardial oxygen demand, which helps control angina and ischemia. If the symptoms and signs of heart failure are controlled, an effort should be made to use beta blockers not only for angina but because trials in heart failure have shown significant improvement in survival. A trial of the intravenous ultra-short-acting beta blocker esmolol may be useful to establish the safety of beta blockade in selected patients. Nocturnal angina often can be relieved by the treatment of heart failure.

The combination of congestive heart failure and angina in patients with IHD usually indicates a poor prognosis and warrants serious consideration of cardiac catheterization and coronary revascularization.

CORONARY REVASCUARIZATION

Clinical trials have confirmed that with the initial diagnosis of stable IHD, it is first appropriate to initiate a medical regimen as described above. Revascularization should be considered in the presence of unstable phases of the disease, intractable symptoms, high-risk coronary anatomy, diabetes, and impaired LV function. *Revascularization should be employed in conjunction with but not replace the continuing*

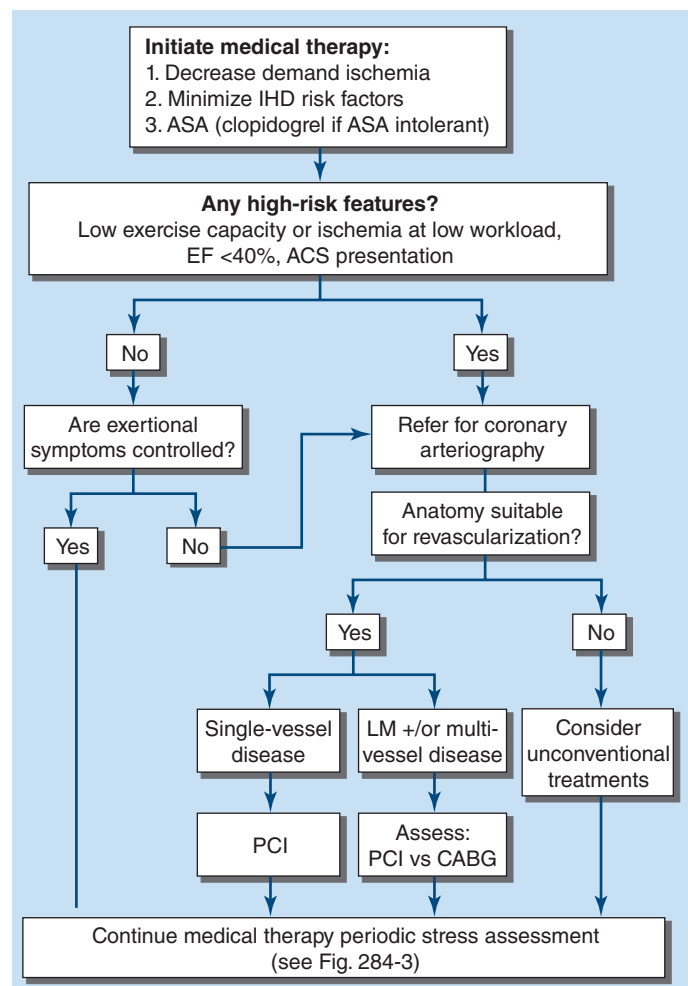


FIGURE 284-4 Algorithm for management of a patient with ischemic heart disease. All patients should receive the core elements of medical therapy as shown at the top of the algorithm. If high-risk features are present, as established by the clinical history, exercise test data, and imaging studies, the patient should be referred for coronary arteriography. Based on the number and location of the diseased vessels and their suitability for revascularization, the patient is treated with a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or should be considered for unconventional treatments. See text for further discussion. ACS, acute coronary syndrome; ASA, aspirin; EF, ejection fraction; IHD, ischemic heart disease; LM, left main.

need to modify risk factors and assess medical therapy. An algorithm for integrating medical therapy and revascularization options in patients with IHD is shown in [Fig. 284-4](#).

■ PERCUTANEOUS CORONARY INTERVENTION

(See also [Chap. 287](#)) PCI involving balloon dilatation usually accompanied by coronary stenting is widely used to achieve revascularization of the myocardium in patients with symptomatic IHD and suitable stenoses of epicardial coronary arteries. Whereas patients with stenosis of the left main coronary artery and those with three-vessel IHD (especially with diabetes and/or impaired LV function) who require revascularization are best treated with CABG, PCI is widely employed in patients with symptoms and evidence of ischemia due to stenoses of one or two vessels and even in selected patients with three-vessel disease (and, perhaps, in some patients with left main disease) and may offer many advantages over surgery.

Indications and Patient Selection The most common clinical indication for PCI is symptom-limiting angina pectoris, despite medical therapy, accompanied by evidence of ischemia during a stress test. PCI is more effective than medical therapy for the relief of angina. PCI improves outcomes in patients with unstable angina or when used early in the course of myocardial infarction with and without cardiogenic shock. However, in patients with stable exertional angina, clinical trials

have confirmed that PCI does not reduce the occurrence of death or myocardial infarction compared to optimum medical therapy. PCI can be used to treat stenoses in native coronary arteries as well as in bypass grafts in patients who have recurrent angina after CABG.

Risks When coronary stenoses are discrete and symmetric, two and even three vessels can be treated in sequence. However, case selection is essential to avoid a prohibitive risk of complications, which are usually due to dissection or thrombosis with vessel occlusion, uncontrolled ischemia, and ventricular failure (**Chap. 287**). Oral aspirin, a P2Y₁₂ antagonist, and an antithrombin agent are given to reduce coronary thrombus formation. Left main coronary artery stenosis generally is regarded as a lesion that should be treated with CABG. In selected cases such as patients with prohibitive surgical risks, PCI of an unprotected left main can be considered, but such a procedure should be performed only by a highly skilled operator; importantly, there are regional differences in the use of this approach internationally.

Efficacy Primary success, with relief of angina, is achieved in >95% of cases. In diseased vein grafts, procedural success has been improved by the use of an embolic protection device, when feasible, to prevent ischemia and infarction. The use of current-generation drug-eluting stents that locally deliver antiproliferative drugs have a lower rate of restenosis (<5%) than the initial bare metal stents and are now the standard of care in PCI. Of note, however, the delayed endothelial healing in the region of a drug-eluting stent also extends the period during which the patient is at risk for subacute stent thrombosis. Aspirin should be administered indefinitely and a P2Y₁₂ antagonist daily (dual antiplatelet therapy [DAPT]) ideally for 1 year after implantation of a drug-eluting stent. Evidence exists of a benefit of continuing DAPT for up to 30 months, albeit at the cost of a higher risk of bleeding. Shorter courses of DAPT may be used in patients who are at high bleeding risk (**see Chap. 69**) or who have a long-term indication for oral anticoagulation (**see Chap. 121**).

Efforts are underway to develop new antithrombotic regimens to reduce the risk of bleeding. These include (1) shortening the duration of DAPT by eliminating aspirin after 1 or 3 months and continuing a P2Y₁₂ antagonist alone, (2) de-escalating from a potent P2Y₁₂ inhibitor (i.e., prasugrel, ticagrelor) after 1 month to clopidogrel or reduced-dose prasugrel 5 mg daily, and (3) switching from DAPT to dual pathway inhibition with an antiplatelet agent and a low-dose direct oral anticoagulant. While each of these has been compared to standard DAPT regimens, such studies tend to be unpowered for ischemic events, and these alternative strategies have not been compared to one another.

When a situation arises in which temporary discontinuation of antiplatelet therapy is necessary, the clinical circumstances should be reviewed with the operator who performed the PCI and a coordinated plan should be established for minimizing the risk of late stent thrombus; central to this plan is the discontinuation of antiplatelet therapy for the shortest acceptable period. The risk of stent thrombosis is dependent on stent size and length, complexity of the lesions, age, diabetes, and technique. However, compliance with DAPT and individual responsiveness to platelet inhibition are very important factors as well.

Successful PCI produces effective relief of angina in >95% of cases. The majority of patients with symptomatic IHD who require revascularization can be treated initially by PCI. Successful PCI is less invasive and expensive than CABG and permits savings in the *initial* cost of care. Successful PCI avoids the risk of stroke associated with CABG surgery and allows earlier return to work and resumption of an active life. However, the early health-related and economic benefits of PCI are reduced over time because of the greater need for follow-up and the increased need for repeat procedures. When directly compared in patients with diabetes or three-vessel or left main CAD, CABG was superior to PCI in preventing major adverse cardiac or cerebrovascular events over a 12-month follow-up.

■ CORONARY ARTERY BYPASS GRAFTING

Anastomosis of one or both of the internal mammary arteries or a radial artery to the coronary artery distal to the obstructive lesion is the preferred procedure. For additional obstructions that cannot be bypassed by an artery, a section of a vein (usually the saphenous) is

used to form a venous bypass conduit between the aorta and the coronary artery distal to the obstructive lesion.

Although some indications for CABG are controversial, certain areas of agreement exist:

1. The operation is relatively safe, with mortality rates <1% in patients without serious comorbid disease and normal LV function and when the procedure is performed by an experienced surgical team.
2. Intraoperative and postoperative mortality rates increase with the severity of ventricular dysfunction, comorbidities, age ≥80 years, and lack of surgical experience. The effectiveness and risk of CABG vary widely depending on case selection and the skill and experience of the surgical team.
3. Occlusion of *venous* grafts is observed in 10–20% of patients during the first postoperative year and in ~2% per year during 5- to 7-year follow-up and 4% per year thereafter. Long-term patency rates are considerably higher for internal mammary and radial artery implantations than for saphenous vein grafts. In patients with left anterior descending coronary artery obstruction, survival is better when coronary bypass involves the internal mammary artery rather than a saphenous vein. Graft patency and outcomes are improved by meticulous treatment of risk factors, particularly dyslipidemia.
4. Angina is abolished or greatly reduced in ~90% of patients after complete revascularization. Although this usually is associated with graft patency and restoration of blood flow, the pain may also have been alleviated as a result of infarction of the ischemic segment, denervation due to median sternotomy, or a placebo effect.
5. Survival may be improved by operation in patients with stenosis of the left main coronary artery as well as in patients with three- or two-vessel disease with significant obstruction of the proximal left anterior descending coronary artery. The survival benefit is greater in patients with abnormal LV function (ejection fraction <35). Survival *may* also be improved in the following patients: (a) patients with obstructive CAD who have survived sudden cardiac death or sustained ventricular tachycardia; (b) patients who have undergone previous CABG and have multiple saphenous vein graft stenoses, especially of a graft supplying the left anterior descending coronary artery; and (c) patients with recurrent stenosis after PCI and high-risk criteria on noninvasive testing.
6. Minimally invasive CABG through a small thoracotomy and/or off-pump surgery can reduce morbidity and shorten convalescence in suitable patients but does not appear to reduce significantly the risk of neurocognitive dysfunction postoperatively.
7. Among patients with type 2 diabetes mellitus and multivessel coronary disease, CABG surgery plus optimal medical therapy is superior to optimal medical therapy alone in preventing major cardiovascular events, a benefit mediated largely by a significant reduction in nonfatal myocardial infarction. The benefits of CABG are especially evident in patients with diabetes mellitus treated with an insulin-sensitizing strategy as opposed to an insulin-providing strategy. CABG has also been shown to be superior to PCI (including the use of drug-eluting stents) in preventing death, myocardial infarction, and repeat revascularization in patients with diabetes mellitus and multivessel IHD.

Indications for CABG usually are based on the severity of symptoms, coronary anatomy, and ventricular function. The ideal candidate has no other complicating disease and has troublesome or disabling angina that is not adequately controlled by medical therapy or does not tolerate medical therapy. Great symptomatic benefit can be anticipated if a patient wishes to lead a more active life and has severe stenoses of two or three epicardial coronary arteries with objective evidence of myocardial ischemia as a cause of the chest discomfort. Congestive heart failure and/or LV dysfunction, advanced age (≥80 years), reoperation, urgent need for surgery, and the presence of diabetes mellitus are all associated with a higher perioperative mortality rate.

LV dysfunction can be due to noncontractile or hypocontractile segments that are viable but are chronically ischemic (hibernating myocardium). As a consequence of chronic reduction in myocardial blood flow, these segments downregulate their contractile function.

They can be detected by using radionuclide scans of myocardial perfusion and metabolism, PET, cardiac MRI, or delayed scanning with thallium-201 or by improvement of regional functional impairment provoked by low-dose dobutamine. In such patients, revascularization improves myocardial blood flow, can return function, and can improve survival.

The Choice Between PCI and CABG All the clinical characteristics of each individual patient must be used to decide on the method of revascularization (e.g., LV function, diabetes, lesion complexity). A number of randomized clinical trials have compared PCI and CABG in patients with multivessel CAD who were suitable technically for both procedures. The redevelopment of angina requiring repeat coronary angiography and repeat revascularization is higher with PCI. This is a result of restenosis in the stented segment (a problem largely solved with drug-eluting stents) and the development of new stenoses in unstented portions of the coronary vasculature. It has been argued that PCI with stenting focuses on culprit lesions, whereas a bypass graft to the target vessel also provides a conduit around future culprit lesions proximal to the anastomosis of the graft to the native vessel (Fig. 284-5). By contrast, stroke rates are lower with PCI.

Based on available evidence, it is now recommended that patients with lifestyle-limiting angina despite guideline-directed medical management and therapy be considered for coronary revascularization. Patients with single- or two-vessel disease with normal LV function and anatomically suitable lesions ordinarily are advised to undergo PCI (Chap. 287). For patients who are poor candidates for surgery, it is reasonable to choose PCI over CABG to improve symptoms and reduce major adverse cardiac events.

In patients with left main disease associated with high-complexity CAD, CABG remains preferred to PCI to improve survival. Similarly, in patients with diabetes and multivessel disease involving the left anterior descending artery, CABG (with a left internal mammary conduit) is preferred over PCI, although in patients with low- or intermediate-complexity CAD, PCI may be considered.

Patients with three-vessel disease (or two-vessel disease that includes the proximal left descending coronary artery) and impaired global LV function (LV ejection fraction <50%) or diabetes mellitus and those with left main CAD or other lesions unsuitable for catheter-based procedures should be considered for CABG as the initial method of revascularization. In light of the complexity of the decision-making, it is desirable to have a multidisciplinary team, including a cardiologist and a cardiac surgeon in conjunction with the patient's primary care physician, provide input along with ascertaining the patient's preferences before committing to a particular revascularization option.

■ UNCONVENTIONAL TREATMENTS FOR IHD

On occasion, clinicians will encounter a patient who has persistent, disabling angina despite maximally tolerated medical therapy and for whom revascularization is not an option (e.g., small diffusely diseased vessels not amenable to stent implantation or acceptable targets for bypass grafting). In such situations, unconventional treatments should be considered.

Enhanced external counterpulsation utilizes pneumatic cuffs on the lower extremities to provide diastolic augmentation and systolic unloading of blood pressure to decrease cardiac work and oxygen consumption while enhancing coronary blood flow. Clinical trials have shown that regular application improves angina, exercise capacity, and regional myocardial perfusion.

Neuromodulation (e.g., spinal cord stimulation, transcutaneous or subcutaneous electrical neural stimulation, sympathectomy) and

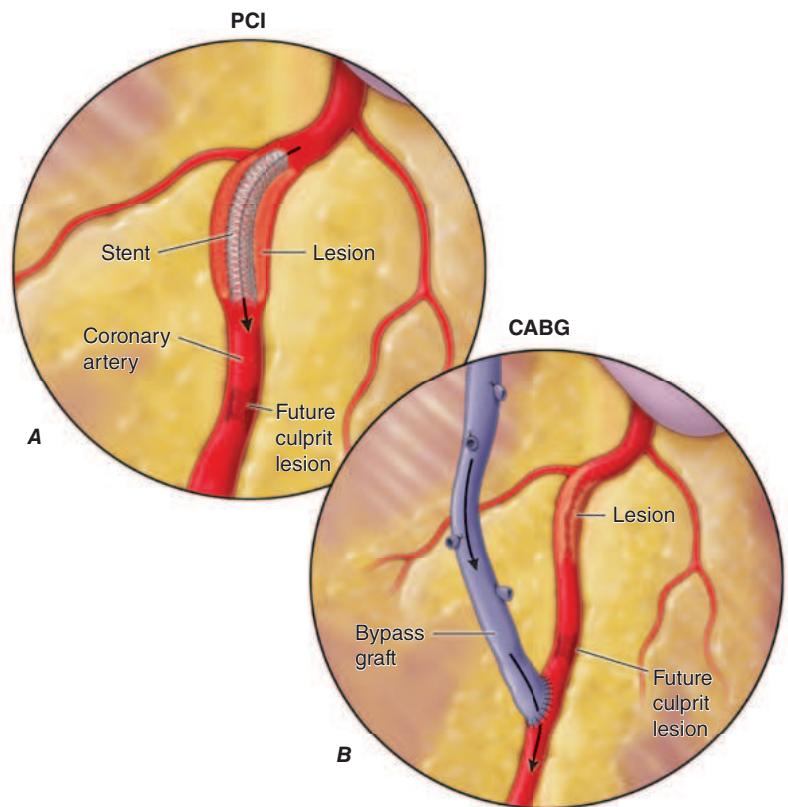


FIGURE 284-5 Difference in the approach to the lesion with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). PCI is targeted at the “culprit” lesion or lesions, whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions and future culprits, proximal to the insertion of the vein graft, a difference that may account for the superiority of CABG, at least in the intermediate term, in patients with multivessel disease. (From *The New England Journal of Medicine, Quantitative Determinants of the Outcome of Asymptomatic Mitral Regurgitation*, M Enriquez-Sarano et al. 352, 2235. Copyright © 2005. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

coronary sinus constriction (using a reducer device) have shown promise in small studies. Experimental approaches, such as stem cell therapies and cardiac repair with small noncoding RNA molecules (miRNA), are also under active study.

ASYMPTOMATIC (SILENT) ISCHEMIA

Obstructive CAD, acute myocardial infarction, and transient myocardial ischemia can occur in the absence of symptoms. During continuous ambulatory ECG monitoring, the majority of ambulatory patients with typical chronic stable angina are found to have objective evidence of myocardial ischemia (ST-segment depression) during episodes of chest discomfort while they are active outside the hospital. In addition, many of these patients also have more frequent episodes of asymptomatic ischemia. Frequent episodes of ischemia (symptomatic and asymptomatic) during daily life appear to be associated with an increased likelihood of adverse coronary events (death and myocardial infarction). In addition, patients with asymptomatic ischemia after a myocardial infarction are at greater risk for a second coronary event. The widespread use of exercise ECG during routine examinations has also identified some of these previously unrecognized patients with asymptomatic CAD. Longitudinal studies have demonstrated an increased incidence of coronary events in asymptomatic patients with positive exercise tests.

TREATMENT

Asymptomatic Ischemia

The management of patients with asymptomatic ischemia must be individualized. When coronary disease has been confirmed, the aggressive treatment of hypertension and dyslipidemia is essential and will decrease the risk of infarction and death. In addition, the physician should consider the following: (1) the degree of positivity

of the stress test, particularly the stage of exercise at which ECG signs of ischemia appear; the magnitude and number of the ischemic zones of myocardium on imaging; and the change in LV ejection fraction that occurs on radionuclide ventriculography or echocardiography during ischemia and/or during exercise; (2) the ECG leads showing a positive response, with changes in the anterior precordial leads indicating a less favorable prognosis than changes in the inferior leads; and (3) the patient's age, occupation, and general medical condition.

Most would agree that an asymptomatic 45-year-old commercial airline pilot with significant (0.4-mV) ST-segment depression in leads V_1 to V_4 during mild exercise should undergo coronary arteriography, whereas an asymptomatic, sedentary 85-year-old retiree with 0.1-mV ST-segment depression in leads II and III during maximal activity need not. However, there is no consensus about the most appropriate approach in the large majority of patients for whom the situation is less extreme. Asymptomatic patients with silent ischemia, three-vessel CAD, and impaired LV function may be considered appropriate candidates for CABG.

The treatment of risk factors, particularly lipid lowering and blood pressure control as described above, and the use of aspirin, statins, and beta blockers after infarction have been shown to reduce events and improve outcomes in asymptomatic as well as symptomatic patients with ischemia and proven CAD. Although the incidence of asymptomatic ischemia can be reduced by treatment with beta blockers, calcium channel blockers, and long-acting nitrates, it is not clear whether this is necessary or desirable in patients who have not had a myocardial infarction.

FURTHER READING

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285

Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina)

Robert P. Giugliano, Christopher P. Cannon, Eugene Braunwald

Patients with acute coronary syndrome (ACS) are commonly classified into two groups to facilitate evaluation and management, namely patients with acute myocardial infarction (MI) with ST-segment elevation (STEMI) on their presenting electrocardiogram (ECG) (see Chap. 286) and those with non-ST-segment elevation acute coronary syndrome (NSTEMI). The latter include patients with non-ST-segment elevation MI (NSTEMI), who, by definition, have evidence of myocyte necrosis, and those with unstable angina (UA), who do not (Fig. 285-1).

The incidence of NSTEMI is rising due to the increasing burden of obesity, diabetes, and chronic kidney disease in an aging population and the increasing detection of myocardial necrosis by troponin (see below), whereas the incidence of STEMI is declining due to greater use of aspirin, statins, and less smoking. Among patients with NSTEMI-ACS, the proportion with NSTEMI is increasing while that with UA is falling because of the wider use of highly sensitive troponin (hsTn) assays (see below) with enhanced detection of myocyte necrosis, thereby reclassifying UA to NSTEMI.

PATHOPHYSIOLOGY

NSTEMI-ACS is caused by an imbalance between myocardial oxygen supply and demand, most commonly resulting from one or more of three processes that lead to coronary arterial thrombosis: (1) plaque fissure with inflammation—the inflammatory response is reflected by an increased activity of effector T cells as part of an adaptive immunity dysregulation; (2) plaque fissure without inflammation; and (3) plaque erosion, which is present in at least one-third of ACS and is recognized with increasing frequency (Fig. 285-2). The so-called “vulnerable plaques” responsible for ACS may show an eccentric stenosis with scalloped or overhanging edges and a narrow neck on coronary angiography. Such plaques usually are composed of a lipid-rich core with a thin fibrous cap. Patients with NSTEMI-ACS frequently have multiple such plaques that are at risk of disruption. A fourth process, without thrombosis, may be caused by epicardial or microvascular spasm or increased myocardial oxygen demand, typically in the presence of fixed epicardial coronary obstruction.

Among patients with NSTEMI-ACS studied at angiography, <10% have stenosis of the left main coronary artery, and approximately 35% have three-vessel coronary artery disease, 25% have two-vessel disease, 20% have single-vessel disease, and 10% have no apparent critical epicardial coronary artery stenosis; some of the latter may have obstruction of the coronary microcirculation and/or spasm of the epicardial vessels.

CLINICAL PRESENTATION

Diagnosis The diagnosis of NSTEMI-ACS is based largely on a combination of the history and clinical findings (age, ECG, and circulating troponin) (Table 285-1, Fig. 285-3).

History and Physical Examination Typically, chest discomfort is severe and has at least one of three features: (1) occurrence at rest (or with minimal exertion), lasting >10 min; (2) of relatively recent onset (i.e., within the prior 2 weeks); and/or (3) a crescendo pattern, i.e., distinctly more severe, prolonged, or frequent than previous episodes.

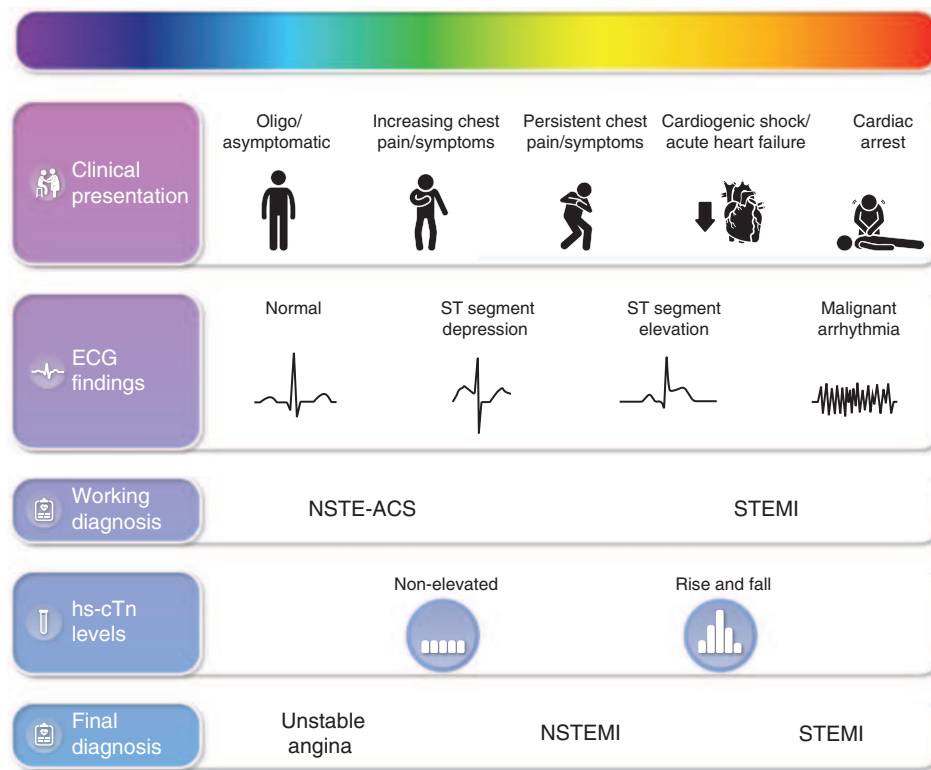


FIGURE 285-1 Spectrum of acute coronary syndromes. The spectrum of clinical presentations, electrocardiographic findings, and high-sensitivity cardiac troponin levels in patients with acute coronary syndrome. ACS, acute coronary syndrome; ECG, electrocardiogram; hs-cTn, high-sensitivity cardiac troponin; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction. (RA Byrne et al: 2023 ESC guideline for the management of acute coronary syndromes. Eur Heart J 44:3720, 2023, by permission of Oxford university Press.)

The diagnosis of NSTEMI is established if a patient with any of these features (without ECG ST-segment elevations) develops evidence of myocardial necrosis, as reflected in abnormally elevated levels of circulating troponin, in the absence of another explanation (see below). The

chest discomfort is typically located in the substernal region and radiates to the left arm, left shoulder, and/or superiorly to the neck and jaw. Anginal equivalents such as dyspnea, epigastric discomfort, nausea, or weakness may occur instead of chest discomfort. These equivalents are more frequently reported by women, the elderly, and patients with diabetes mellitus. The physical examination resembles that in patients with stable angina (see Chap. 284) and may be unremarkable. However, if the patient has a large area of myocardial ischemia or a large NSTEMI, the physical findings can include diaphoresis; pale, cool skin; sinus tachycardia; a third and/or fourth heart sound; basilar rales; hypotension; and in severe cases, cardiogenic shock. An important goal of the physical examination is to identify potential alternative life-threatening diagnoses, e.g., pulmonary embolism (see Chap. 290), aortic dissection (see Chap. 291), and cardiac tamponade (see Chap. 281),

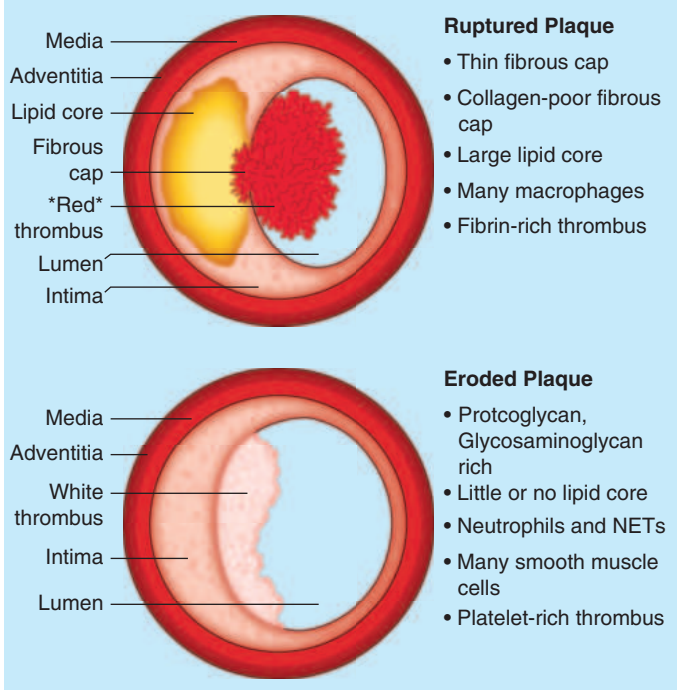


FIGURE 285-2 Comparison of the characteristics of human atheromata complicated by thrombosis and causing acute coronary syndrome. The column on the left highlights some of the characteristics demonstrated by analyses of human coronary arterial lesions that have undergone thrombosis by these two diverse mechanisms. NETs, neutrophil extracellular traps. (Reproduced with permission from P Libby et al: Reassessing the mechanisms of acute coronary syndromes the “vulnerable plaque” and superficial erosion. Circ Res 124:150, 2019.)

TABLE 285-1 TIMI Risk Score for NSTE-ACS	
RISK MARKERS	
- Age ≥ 65 years - Known CAD ($\geq 50\%$ stenosis) - ST deviation >0.5 mm on presenting ECG	$\uparrow$ cardiac markers ≥ 2 original episodes in prior 24 h - Prior angina ≥ 3 CAD risk factors
NO. OF RISK MARKERS	INCIDENCE OF ADVERSE CARDIAC EVENTS ^a (%)
0/1	5
2	8
3	13
4	20
5	26
6/7	41

^aRisk at 14 days of death, new or recurrent myocardial infarction, or severe recurrent ischemia requiring urgent revascularization.
Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; TIMI, Thrombolysis in Myocardial Infarction.

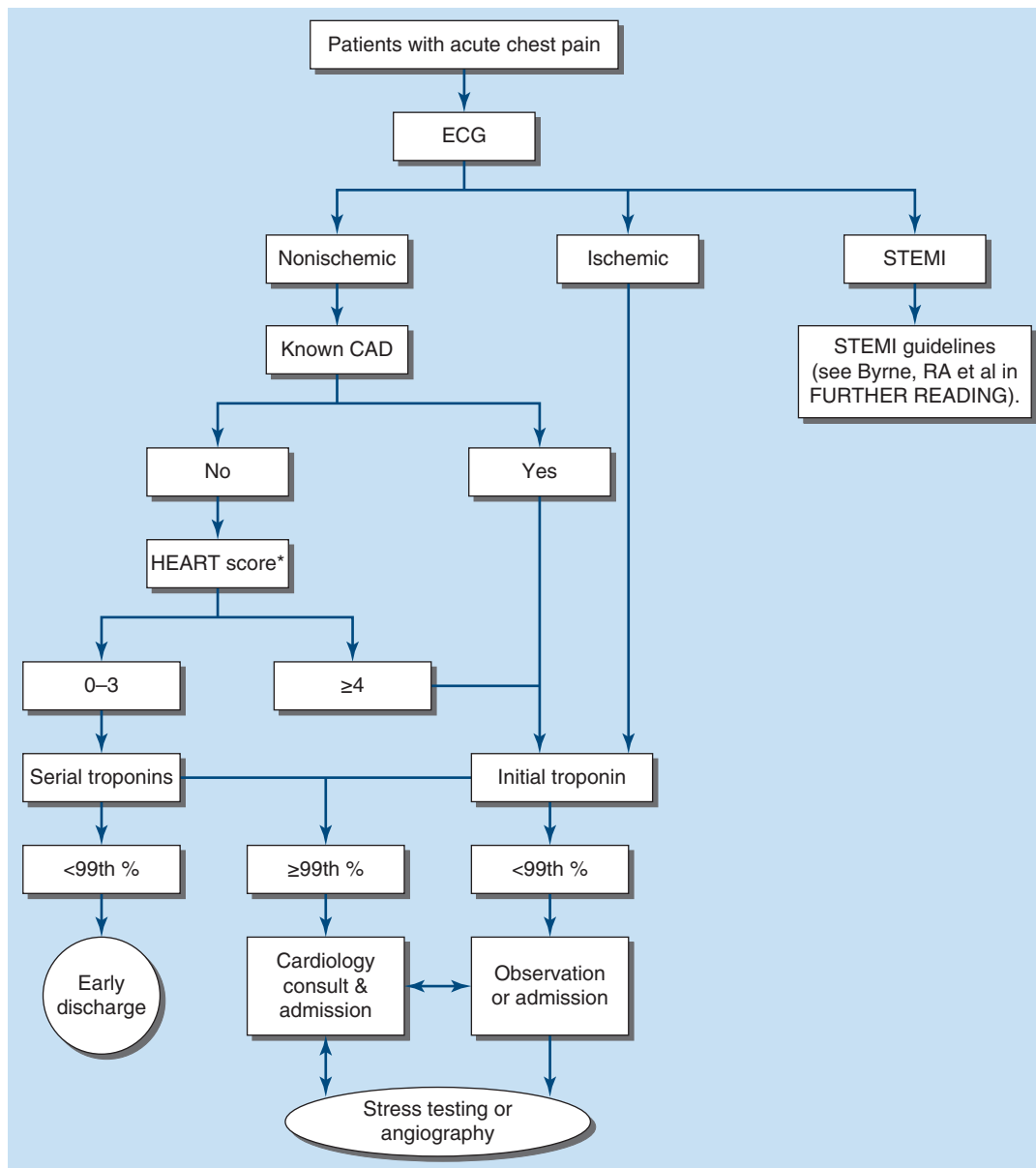


FIGURE 285-3 The HEART pathway for evaluation of acute chest pain. CAD, coronary artery disease; ECG, electrocardiogram; STEMI, ST-segment elevation myocardial infarction. *The Heart Score assigns 0, 1, or 2 points depending on the extent of abnormality for each of the History, ECG, Age, Risk factors, and Troponin (Six AJ, Backus BE, and Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J* 16:191, 2008). (Reproduced with permission from JL Januzzi et al: Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC scientific expert panel. *J Am Coll Cardiol* 73:1059-1077, 2019.)

given the vastly different treatment plans required to avoid major morbidity and death.

Electrocardiogram New ST-segment depression occurs in about one-third of patients with NSTEMI-ACS. It may be transient but can persist for as long as several days following NSTEMI. T-wave changes are more common but are a less specific sign of ischemia unless they are new and deep T-wave inversions (≥ 0.3 mV).

Cardiac Biomarkers Patients with NSTEMI have elevated biomarkers of necrosis, such as cardiac troponin (cTn) I or T (cTnI or cTnT). High-sensitive (hs) cTns are sensitive, relatively specific, and the preferred markers of myocardial necrosis. Elevated levels of cTn with a dynamic early change distinguish patients with NSTEMI from those with UA. In patients with NSTEMI, there is a characteristic temporal rise of the plasma concentration, peaking at 12–24 h after onset of symptoms and gradually decreasing thereafter. There is a direct relationship between the degree of elevation and mortality. The 1-h rapid rule-out MI algorithm (no abnormal elevation of hsTn at 0 or 1 h after presentation) has been recommended by recent practice guidelines. It is important to distinguish myocardial injury from myocardial

necrosis; the former is defined by elevations of cTn >99 th percentile of the upper reference limit in patients *without* a clear clinical history or ECG features of acute myocardial ischemia. Myocardial injury may be caused by a variety of noncardiac and cardiac conditions other than MI (Table 285-2).

RISK STRATIFICATION

Patients with documented NSTEMI-ACS exhibit a wide spectrum of early (30 days) risk of death, ranging from 1 to 10%, and a recurrent ACS rate of 5–15% during the first year. Assessment of risk can be accomplished by one of several clinical risk scoring systems, including those developed from the Thrombolysis in Myocardial Infarction (TIMI) Trials, the Global Registry of Acute Coronary Event (GRACE), and the HEART (history, electrocardiogram, age, risk factors, troponin) score (Fig. 285-3). Multimarker strategies including hsTn and brain natriuretic peptides are now gaining favor, both to define more fully the pathophysiologic mechanisms underlying a patient's presentation and to stratify the patient's risk further. Early risk assessment is useful in identifying patients who would derive the greatest benefit from an early invasive strategy (see below).

TABLE 285-2 Reasons for the Elevation of Cardiac Troponin Values as a Result of Myocardial Injury**Myocardial injury related to acute myocardial infarction**

Atherosclerotic plaque disruption or erosion with thrombosis

Myocardial injury related to acute myocardial ischemia because of oxygen supply/demand imbalance*Reduced myocardial perfusion*

- Coronary artery spasm, microvascular dysfunction
- Coronary embolism
- Coronary artery dissection
- Sustained bradyarrhythmia
- Hypotension or shock
- Respiratory failure
- Severe anemia

Increased myocardial oxygen demand

- Sustained tachyarrhythmia
- Severe hypertension

Other causes of myocardial injury*Cardiac conditions*

- Heart failure
- Myocarditis
- Cardiomyopathy (any type)
- Takotsubo syndrome
- Recent coronary revascularization
- Cardiac procedure other than revascularization
- Catheter ablation
- Defibrillator shocks
- Cardiac contusion

Systemic conditions

- Sepsis
- Chronic kidney disease
- Stroke, subarachnoid hemorrhage
- Pulmonary embolism
- Infiltrative diseases, e.g., amyloidosis, sarcoidosis
- Chemotherapeutic agents
- Critical illness
- Strenuous exercise

Note: For a more comprehensive listing, see the Fourth Universal Definition of Myocardial Infarction (source).

Source: Reproduced with permission from K Thygesen et al: Fourth universal definition of myocardial infarction (2018). *Circulation* 138:2231, 2018.

TREATMENT**Non-ST-Segment Elevation Acute Coronary Syndrome**

Patients with a low likelihood of ischemia can usually be managed in an emergency department or a dedicated “chest pain unit.” Evaluation of such patients includes clinical monitoring for recurrent ischemic discomfort and continuous monitoring of ECGs, serial monitoring of hsTn at presentation, 1 h, and, if necessary, 3 h. In patients for whom there is diagnostic uncertainty or intermediate-risk patients, stress testing to detect and grade ischemia or cardiac computed tomography angiography to assess epicardial coronary artery obstruction may be considered ([see Chaps. 248 and 284](#)).

MEDICAL TREATMENT

Patients who “rule-in” for NSTEMI-ACS by clinical features, hsTn, or ST-T-wave changes on the ECG should be admitted to the hospital. Patients should be placed on bed rest with continuous ECG monitoring for ST-segment deviation and cardiac arrhythmias, preferably on a specialized cardiac unit. Ambulation is permitted if the patient shows no recurrence of ischemia (symptoms or ECG changes) and does not develop an elevation of cTn for 24 h.

Medical therapy consists of an acute phase focused on the clinical symptoms and stabilization of the culprit lesion(s) and a longer-term phase that involves therapies directed at the prevention of disease progression and future recurrent NSTEMI-ACS.

ANTI-ISCHEMIC TREATMENT (TABLE 285-3)

To provide relief of pain and discomfort, initial treatment, in addition to bed rest, includes nitrates, β -adrenergic blockers, and inhaled oxygen in patients with hypoxemia (arterial O₂ saturation <90%) and/or in those with heart failure and rales.

Nitrates Nitroglycerin should first be given sublingually or by buccal spray (0.3–0.6 mg) if the patient is experiencing ischemic discomfort. If symptoms persist after three doses given 5 min apart, intravenous nitroglycerin (5–10 μ g/min, using nonabsorbing tubing) is recommended. The infusion rate may be increased by 10 μ g/min every 3–5 min until symptoms are relieved, systolic arterial pressure falls to <90 mmHg, or the dose reaches 200 μ g/min. Topical or oral nitrates ([see Chap. 284](#)) can be used when the pain has resolved, or they may replace intravenous nitroglycerin when the patient has been symptom-free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension or the recent use of a phosphodiesterase type 5 (PDE-5) inhibitor, sildenafil or vardenafil (within 24 h), or tadalafil (within 48 h).

β -Adrenergic Blockers and Other Agents Beta blockers are the other mainstay of anti-ischemic treatment because they reduce myocardial oxygen needs. They may be started by the intravenous route in patients with severe ischemia but should be avoided in the presence of acute or severe heart failure, low cardiac output,

TABLE 285-3 Recommendations for Anti-Ischemic Drugs in the Acute Phase of NSTEMI-ACS

THERAPY	RECOMMENDATION	WHEN TO AVOID
Nitrates	• Use sublingual or intravenous nitrates to relieve angina • Use intravenous nitrates if recurrent angina, uncontrolled hypertension, or signs of heart failure • Consider in patients with vasospastic angina	• Recent use of a PDE-5 inhibitor^a • Hypotension • Right ventricular infarct • Severe aortic stenosis
Beta blockers	• Initiate early for ischemic symptoms • Continue chronic therapy	• PR interval >0.24 s • 2nd or 3rd atrioventricular block • Heart rate <50 beats/min • Systolic pressure <90 mmHg • Shock or Killip class III or IV heart failure • Severe reactive airways disease
Calcium channel blockers	• Consider in patients with vasospastic angina • Consider in patients with contraindications to beta blockers	• Systolic pressure <90 mmHg • Pulmonary edema • Left ventricular dysfunction^b • Avoid short-acting nifedipine
Morphine or other narcotic analgesics ^c	• Continued severe angina despite 3 sublingual nitroglycerin tablets • Recurrent ischemia despite adequate anti-ischemic therapy	• Hypotension • Respiratory depression • Confusion or obtundation

^aSildenafil or vardenafil <24 h or tadalafil <48 h. ^bDiltiazem or verapamil.

^cConcomitant administration may delay the absorption and blunt the antiplatelet effect of oral P2Y₁₂ inhibitors.

Abbreviations: NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; PDE-5, phosphodiesterase type 5.

Source: Modified from M Roffi et al: *Eur Heart J* 37:267, 2017.

hypotension, or contraindications (e.g., high-degree atrioventricular block, active bronchospasm). Ordinarily, oral beta blockade targeted to a heart rate of 50–60 beats/min is recommended.

Heart rate–slowing calcium channel blockers, e.g., verapamil or diltiazem, are recommended for patients who have persistent symptoms or ECG signs of ischemia after treatment with full-dose nitrates and beta blockers and in patients with contraindications to either class of these agents. Patients who have continuing severe chest pain despite maximal anti-ischemic therapy and are without contraindications to morphine may receive this drug intravenously (1–5 mg every 5–30 min). Additional medical therapy includes angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Early administration of intensive HMG-CoA reductase inhibitors (statins), such as atorvastatin 80 mg/d or rosuvastatin 40 mg/d, prior to percutaneous coronary intervention (PCI), and continued thereafter has been shown to reduce both early and late recurrent ischemic events. In patients who do not have an adequate response to maximally tolerated statin (i.e., <50% decrease in low-density lipoprotein cholesterol [LDL-C]), addition of ezetimibe 10 mg daily and/or a PCSK9 inhibitor (alirocumab, evolocumab) early after ACS have been shown to further reduce the LDL-C and prevent future cardiovascular events.

ANTITHROMBOTIC THERAPY

Antithrombotic therapy consisting of antiplatelet and anticoagulant drugs represents the second major cornerstone of treatment (Table 285-4).

Antiplatelet Drugs (See Chap. 123) Initial treatment should begin with the cyclooxygenase inhibitor aspirin with a dose of 150–325 mg of an oral non-enteric-coated preparation or 75–250 mg intravenously. Thereafter, lower oral doses (75–100 mg/d) are recommended since they maintain efficacy while causing less bleeding. Contraindications are severe active bleeding and aspirin allergy.

In the absence of a high risk for bleeding, patients with NSTEMI-ACS, irrespective of whether an invasive or conservative strategy (see below) is selected, should also receive a platelet P2Y₁₂ receptor blocker to inhibit platelet activation. There are now three oral and one intravenous P2Y₁₂ inhibitors available. The thienopyridine clopidogrel is an inactive prodrug that is converted into an active metabolite that causes irreversible blockade of the platelet P2Y₁₂ receptor. The loading dose of clopidogrel is 300–600 mg, whereas the maintenance dose is 75 mg daily. When clopidogrel is added to aspirin, so-called dual antiplatelet therapy (DAPT), in patients with NSTEMI-ACS, it confers a 20% relative reduction in cardiovascular death, MI, or stroke, compared to aspirin alone but is associated with a moderate (absolute 1%) increase in major bleeding.

Two other P2Y₁₂ inhibitors have been shown to be superior to clopidogrel in preventing recurrent cardiac ischemic events but both increase bleeding. Prasugrel, also a thienopyridine, achieves a more rapid onset and higher level of irreversible platelet inhibition than clopidogrel. Compared to clopidogrel, prasugrel significantly reduced the combined risk of cardiovascular death, MI, stroke, and stent thrombosis, but increased bleeding, in patients with ACS with scheduled PCI. It has been approved for ACS patients following angiography when PCI is planned; it should be administered at a loading dose of 60 mg followed by 10 mg/d. Prasugrel is contraindicated in patients with prior stroke or transient ischemic attack or at high risk for bleeding, and should be administered once the coronary anatomy is known (i.e., post coronary angiography).

Ticagrelor, a potent, reversible platelet P2Y₁₂ inhibitor, reduces the risk of cardiovascular death, total mortality, or MI compared to clopidogrel across a broad spectrum of patients with ACS. After a loading dose of 180 mg, 90 mg bid is administered as maintenance. Like prasugrel, ticagrelor increases the risk of bleeding. Unlike prasugrel, ticagrelor demonstrated benefit whether patients were managed conservatively or with an early invasive strategy (see below). Some patients may develop dyspnea soon after administration, although the symptoms are often transient and infrequently serious.

Up to one-third of patients have an inadequate response to clopidogrel, and a substantial proportion of these cases are related to a

TABLE 285-4 Clinical Use of Antithrombotic Therapy

Oral Antiplatelet Therapy

Aspirin	Loading dose of 150–325 mg orally of nonenteric formulation followed by 75–100 mg/d of an enteric or a nonenteric formulation
Clopidogrel	Loading dose of 600 mg (if PCI planned) or 300 mg (if no PCI planned), followed by 75 mg/d
Prasugrel	Pre-PCI: Loading dose of 60 mg followed by 10 mg/d In patient with body weight <60 kg or >75 years old, maintenance dose of 5 mg/d
Ticagrelor	Loading dose of 180 mg followed by 90 mg twice daily

Intravenous Antiplatelet Therapy at the Time of PCI

Cangrelor	30 µg/kg bolus followed by 4 µg/kg/min infusion for 2 h or duration of procedure
Eptifibatide	180 µg/kg bolus followed in 10 min by second bolus of 180 µg/kg with infusion of 2.0 µg/kg/min for up to 18 h
Tirofiban	25 µg/kg per min over 3 minutes, followed by infusion of 0.15 µg/kg/min for up to 18 h

Parenteral Anticoagulants^a

Unfractionated heparin	Bolus 70–100 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U/kg per h titrated to ACT 250–300 s
Enoxaparin	0.5 mg/kg IV bolus at the time of PCI <i>or</i> 1 mg/kg subcutaneous every 12 h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg once daily if creatine clearance <30 mL/min
Bivalirudin	Initial IV bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg per h
Fondaparinux	2.5 mg subcutaneously daily (only prior to PCI)

Oral Anticoagulant Drugs (concomitant treatment after PCI)

VKA	Dosing based on INR value and the respective clinical indication
Apixaban	Maintenance dose 5 mg (dose reduced to 2.5 mg) twice daily
Dabigatran	Maintenance dose 150 mg (dose reduced to 75 mg) twice daily in the United States; outside the United States, either 110 or 150 mg twice daily may be used
Edoxaban	Maintenance dose 60 mg (dose reduced to 30 mg) once daily
Rivaroxaban	Maintenance dose 20 mg (dose reduced to 15 mg) once daily In patients without atrial fibrillation or venous thromboembolism 2.5 mg bid may be used

Note: All dose reductions for patients meeting criteria. (See also Chap. 123.)

Abbreviations: ACT, activated clotting time; INR, international normalized ratio; PCI, percutaneous coronary intervention; VKA, vitamin K antagonists (e.g., warfarin).

Source: Modified from FJ Neumann: Eur Heart J 40:137, 2019.

genetic variant of the cytochrome P450 system involving the 2C19 gene that leads to reduced conversion of clopidogrel into its active metabolite. Thus, alternate P2Y₁₂ blockers (prasugrel or ticagrelor) should be considered in patients with NSTEMI-ACS who develop a new coronary event while receiving clopidogrel and aspirin. An intravenous, direct, and rapidly acting P2Y₁₂ inhibitor, cangrelor, has also shown benefit relative to clopidogrel in patients who underwent PCI following a NSTEMI-ACS and reduced the risk of cardiovascular ischemic events, but at the expense of increased major bleeding events.

In the 1990s and early 2000s, several trials of glycoprotein IIb/IIIa inhibitors in patients with NSTEMI-ACS had shown modest benefit counterbalanced by an increase in major bleeding. However, the majority of earlier studies were performed without concomitant P2Y₁₂ inhibitor treatment, and more recent studies in patients receiving the latter failed to show a benefit of routine early initiation of a glycoprotein IIb/IIIa inhibitor. Because of the increased risk of bleeding, the addition of a glycoprotein IIb/IIIa inhibitor to aspirin and a P2Y₁₂ inhibitor (i.e., triple antiplatelet therapy) should be reserved for patients undergoing PCI with a high coronary thrombus burden on angiography or thrombotic complications of PCI.

Long-term DAPT should continue preferably for 12 months in patients with NSTEMI-ACS without an indication for long-term

full-dose anticoagulation; the duration of DAPT is dependent upon the risk of bleeding versus thrombosis. Clinicians should select the antiplatelet regimen that provides the best balance between efficacy and safety based on the individual patient characteristics and clinical scenario. A shorter duration of DAPT may be considered for patients at high risk of bleeding who are not high at high ischemic risk (see below). Longer duration DAPT, i.e., >12 months, is favored in patients with high atherothrombotic risk (e.g., due to stenting of the left main coronary artery or proximal left anterior descending or proximal bifurcating coronary arteries, recurrent MI, stent thrombosis).

Anticoagulants (See Chap. 123) Four parenteral options are available for anticoagulant therapy to be added to antiplatelet agents: (1) unfractionated heparin (UFH), long the mainstay of therapy; (2) the low-molecular-weight heparin (LMWH) enoxaparin, which has been shown to be superior to UFH in reducing recurrent cardiac events, especially in patients managed by a conservative strategy (however, it is accompanied by a modest increase in bleeding); (3) bivalirudin, a direct thrombin inhibitor that is similar in efficacy to either UFH or LMWH and is used just prior to and/or during PCI; and (4) fondaparinux, a synthetic factor Xa inhibitor that is equivalent in efficacy to enoxaparin but has a lower risk of major bleeding. While UFH and enoxaparin have been widely studied in patients managed either with an early conservative or invasive strategy, bivalirudin is rarely used in conservatively managed patients, while fondaparinux requires supplemental UFH to prevent procedure-related thrombosis. In patients who develop NSTEMI-ACS while receiving treatment with a direct oral anticoagulant (DOAC), the DOAC (see Chap. 123) should be held when one of the four parenteral anticoagulants is begun.

If an early invasive strategy is indicated (see below), radial arterial access is recommended to reduce the risk of bleeding. Excessive

bleeding is the most important adverse effect of all antithrombotic agents, including both antiplatelet agents and anticoagulants. Therefore, attention must be directed to the doses of antithrombotic agents, accounting for age, body weight, creatinine clearance, and a previous history of excessive bleeding. Patients who have experienced a stroke are at higher risk of intracranial bleeding with potent antiplatelet agents and combinations of antithrombotic drugs. In patients with atrial fibrillation (including patients with NSTEMI-ACS) treated with an oral anticoagulant who undergo PCI, the duration of DAPT should be shortened (e.g., stop aspirin after hospital discharge or at most at 1 month after PCI, except in patients at very high risk for ischemic events), and continue P2Y₁₂ inhibitor plus DOAC for 1 year. After 1 year, the majority of patients should be transitioned to oral anticoagulation monotherapy without concomitant antiplatelet treatment.

INVASIVE VERSUS CONSERVATIVE STRATEGY (FIG. 285-4)

In an invasive strategy, following initiation of anti-ischemic and antithrombotic agents as described above, coronary arteriography is recommended within 2 h of presentation for patients are unstable or within 24 h in high-risk stable patients, followed by coronary revascularization (PCI or coronary artery bypass grafting), depending on the coronary anatomy (Fig. 285-4). Multiple clinical trials have demonstrated the benefit of this strategy in high-risk patients (i.e., patients with multiple clinical risk factors, ST-segment deviation, and/or positive biomarkers). Two studies comparing an immediate invasive strategy (median time to intervention of 1.4 and 4.7 h after presentation) reduced the rate of death or new MI compared to a delayed invasive strategy (median time of intervention of 61 and 62 h), with a greater benefit among patients with a high-risk score. In patients at low risk, the outcomes from an

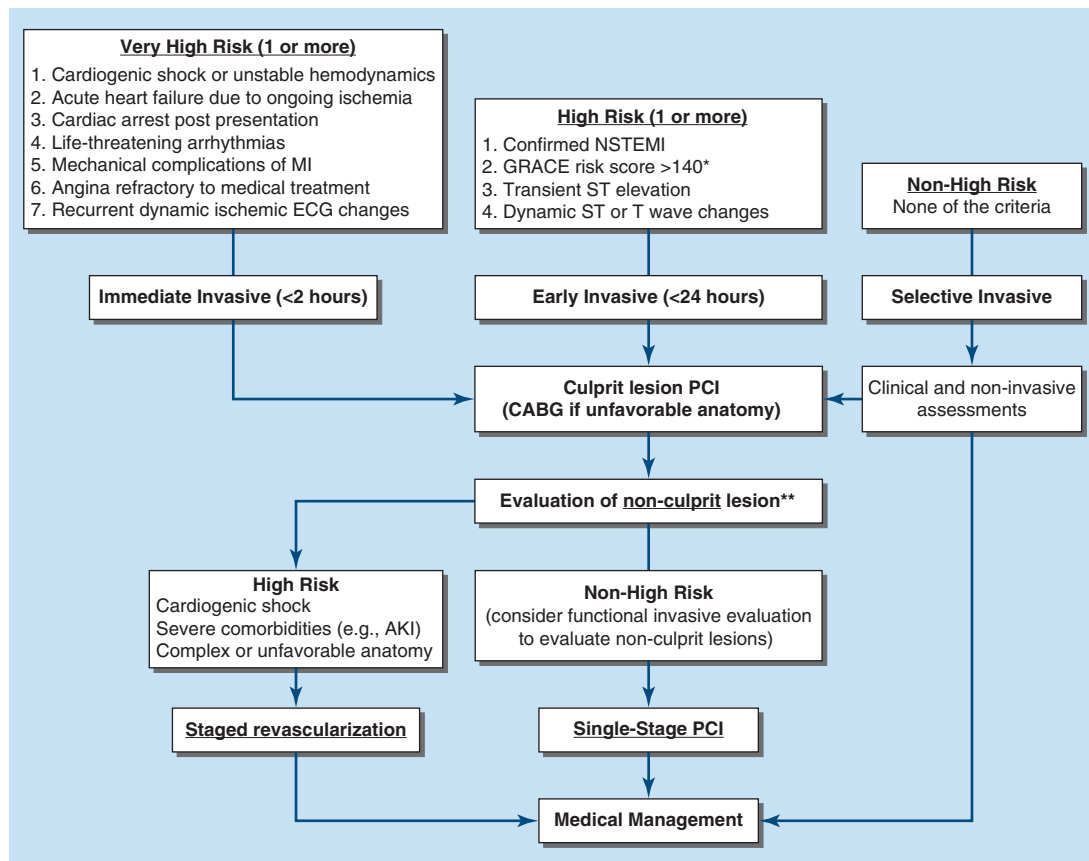


FIGURE 285-4 Selection, timing, and staging of invasive strategy in patients with non-ST-elevation acute coronary syndrome. AKI, acute kidney injury; CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Syndrome Events; PCI, percutaneous coronary intervention. Patients with non-ST-elevations acute coronary syndrome who have one or more very-high risk features should undergo immediate invasive strategy with coronary angiography as soon as possible (within 2 hours), unless absolute contraindications exist. An early invasive strategy should be considered within 24 hours in stable patients with one or more high risk features. Stable patients with no very-high or high risk features should be managed with a selective invasive approach in which clinical, non-invasive assessments, and patient preferences are used to guide management. *Fox KA, BMJ Open 2014;4:e004425. <https://doi.org/10.1136/bmjopen-2013-004425>. **In patients with multivessel disease, single-stage PCI during the index procedure to achieve complete coronary revascularization should be considered in the absence of cardiogenic shock, severe comorbidities such as AKI, or coronary anatomy that is unfavorable or high risk requiring evaluation for The Heart Team for CABG vs complex coronary intervention.

invasive strategy are similar to those obtained from a conservative strategy. The latter consists of anti-ischemic and antithrombotic therapy followed by a “selective invasive approach,” in which the patient is observed closely and coronary arteriography is conducted if coronary computed angiography shows the presence of epicardial coronary stenosis, rest pain or ST-segment changes recur, a biomarker of necrosis becomes positive, or there is evidence of severe ischemia on a stress test.

■ LONG-TERM MANAGEMENT

The time of hospital discharge is a “teachable moment” for the patient with NSTEMI-ACS, when the caregiver can review and optimize the medical regimen. Risk factor modification is crucial, and the importance of smoking cessation, following an appropriate diet, achieving and maintaining optimal weight, daily exercise, an LDL-C <55 mg/dL, blood pressure control, and control of hyperglycemia should be emphasized. There is evidence of benefit with long-term therapy with several classes of drugs. Beta blockers, intensive lipid-lowering therapies (high-intensity statin, ezetimibe, and if needed, adding a PCSK9 inhibitor or bempedoic acid) to achieve an LDL-C <55 mg/dL, ACE inhibitors or angiotensin receptor blockers, and sodium-glucose cotransporter 2 or glucagon-like peptide 1 receptor agonists in selected patients with type 2 diabetes mellitus (see Chap. 416) are recommended. The recommended antiplatelet regimen consists of the combination of low-dose (75–100 mg/d) aspirin and a P2Y₁₂ inhibitor (prasugrel or ticagrelor is favored over clopidogrel) for 12 months unless there is a high risk of bleeding. After 12 months, antiplatelet monotherapy with a single antiplatelet should be continued thereafter (see Chap. 284), unless long-term full-dose anticoagulation is indicated, in which case anticoagulant without antiplatelet therapy is recommended long-term (see above).

Several trials have explored shorter courses and less intensive DAPT in patients not on anticoagulation who are at high risk of bleeding and low risk of ischemic events. Recent guidelines support a shorter-duration DAPT regimens of 3–6 months in these patients, followed by stopping aspirin and continuing with P2Y₁₂ inhibitor alone. Another option is de-escalation of P2Y₁₂ intensity (i.e., switching from prasugrel or ticagrelor to clopidogrel at 3 months) while continuing aspirin. De-escalation of DAPT is not recommended in the first 30 days following ACS as this has been associated with increased risk of ischemic events.

In patients who require long-term anticoagulation (e.g., patients with atrial fibrillation), the duration of so-called “triple therapy” consisting of aspirin, clopidogrel, and an oral anticoagulant should be kept to a minimum. In these patients, aspirin should be discontinued at discharge or 1 week, and oral anticoagulation and clopidogrel continued until month 12, followed thereafter by oral anticoagulant alone. Conversely, in patients at high ischemic risk (e.g., those with prior MI, diabetes mellitus, coronary vein graft, heart failure) who are also at low risk of bleeding and not on an anticoagulant, continuation of DAPT for up to 3 years has been shown to be beneficial. If ticagrelor is used, the dose should be reduced to 60 mg twice daily 1 year after ACS as this reduces bleeding without an increase in ischemic events.

Registries have shown that women and racial minorities, as well as patients with NSTEMI-ACS at high risk, including the elderly and patients with diabetes or chronic kidney disease, are less likely to receive evidence-based pharmacologic and interventional therapies with resultant poorer clinical outcomes and quality of life. Special attention should be directed to these groups.

■ VASOSPASTIC ANGINA

In 1959, Prinzmetal and colleagues described a syndrome of severe ischemic pain that usually occurs at rest and is associated with ST-segment elevation originally known as Prinzmetal’s variant angina, but since renamed vasospastic angina (VA). VA is caused by focal spasm of an epicardial coronary artery with resultant transmural ischemia and abnormalities in left ventricular function that may lead to acute MI, ventricular tachycardia or fibrillation, and sudden cardiac death. The cause of the spasm is not well defined, but it may be related to hypercontractility of coronary arterial smooth muscle due to adrenergic vasoconstrictors, leukotrienes, or serotonin. For reasons that are not

clear, the prevalence of VA has decreased substantially during the past few decades, although it remains much more frequent in Japan than in North America or Western Europe.

Clinical and Angiographic Manifestations Patients with VA are generally younger and, except for cigarette smoking, have fewer coronary risk factors than do patients with NSTEMI-ACS. Cardiac examination is usually unremarkable in the absence of ischemia. However, a minority of patients have a generalized vasospastic disorder associated with migraine and/or Raynaud’s phenomenon. The clinical diagnosis of VA is made by the detection of transient ST-segment elevation with rest pain, although many patients may also exhibit episodes of silent ischemia.

Coronary angiography demonstrates transient coronary spasm as the diagnostic hallmark of VA. Atherosclerotic plaques in at least one proximal coronary artery occur in about half of patients. Hyperventilation and intracoronary acetylcholine have been used to provoke focal coronary stenosis on angiography or to provoke rest angina with ST-segment elevation to establish the diagnosis. In patients with no obstructive coronary atherosclerosis and suspected coronary vasomotor abnormalities, a positive provocative test for spasm has been shown to be safe, identifies a high-risk subgroup, and is endorsed by guidelines since it permits selection of therapy most appropriate for the underlying pathophysiology.

TREATMENT

Vasospastic Angina

Calcium channel blockers are the main therapeutic agents. Nitroglycerin, either sublingual or intravenous, is effective to relieve coronary arterial spasm and angina, but the efficacy of long-term nitrates is limited by nitrate tolerance. Aspirin may actually increase the severity of ischemic episodes, possibly as a result of the sensitivity of coronary tone to modest changes in the synthesis of prostacyclin, and should be used only in patients with significant atherosclerosis. Statin therapy has been shown to reduce the risk of major adverse events, although the precise mechanism is not established. The response to beta blockers is variable. Cilostazol and nicorandil (not available in the United States) may also prevent recurrent episodes. Coronary revascularization may be helpful in patients who also have discrete, flow-limiting, proximal fixed obstructive lesions. Patients who have had ischemia-associated ventricular fibrillation despite maximal medical therapy should receive an implantable cardioverter-defibrillator.

Prognosis Many patients with VA pass through an acute, active phase, with frequent episodes of angina and cardiac events during the first 6 months after presentation, after which there may be a tendency for symptoms and cardiac events to diminish over time. Survival at 5 years is excellent (~90–95%), but as many as 20% of patients experience an MI. Patients with no or mild fixed coronary obstruction experience a lower incidence of cardiac death or MI compared to patients with associated severe obstructive lesions. Patients with VA who develop serious arrhythmias during spontaneous episodes of pain are at a higher risk for sudden cardiac death. In most patients who survive an infarction or the initial 3- to 6-month period of frequent episodes, there is a tendency for symptoms and cardiac events to diminish over time.

■ GLOBAL CONSIDERATIONS

Ischemic heart disease (IHD) and its most dangerous manifestation, ACS, remain the most frequent cause of death and disability worldwide. In the mid-twentieth century, these conditions were most common in high-income countries. Although improvements in primary prevention and treatment of ACS have reduced cardiovascular morbidity and mortality due to IHD over the past 70 years, these advances have not affected all population groups equally. In Europe, there remains a northeast to southwest gradient, with higher prevalence in northern Russia and the Baltic nations and considerably lower prevalence in Spain, France, and Italy. In the United States, there remain racial and economic disparities, with poorer outcomes in minorities and low-income populations.

Simultaneous with these important advances in the high-income countries, the low- and middle-income countries have moved in the opposite direction. Improvements in agriculture, nutrition, sanitation, prevention and treatment of infections, and management of maternal/early childhood disorders, urbanization, and a reduction of physical labor have, in combination, led to marked increases in coronary risk factors—hypertension, cigarette smoking, obesity, diabetes mellitus, and elevations of circulating LDL-C. These changes have been most prominent in Central and South Asia, as well as in the more developed regions of sub-Saharan Africa and the Middle East.

The current challenge is to apply what was learned in high-income countries to the large populations in the low- and middle-income countries that are now at high risk. This will require large educational efforts directed at both the populations and their caregivers. An additional challenge will be to provide the trained specialized personnel, facilities, drugs, and devices to deal with these threats. The successful implementation of these measures is now principally a socio-politico-economic issue. One mitigating factor is that many of the important drugs to prevent and treat these disorders, such as statins, ezetimibe, ACE inhibitors, diuretics, beta blockers, and calcium antagonists, are off patent and are now inexpensive.

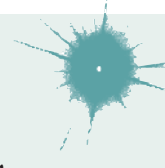
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286

ST-Segment Elevation Myocardial Infarction

David A. Morrow, Elliott M. Antman,
Joseph Loscalzo



Acute myocardial infarction (AMI) is a common diagnosis in hospitalized patients in industrialized countries. In the United States, ~605,000 patients experience a new AMI and 200,000 experience a recurrent AMI each year. About half of AMI-related deaths occur before the stricken individual reaches the hospital. The in-hospital mortality rate after admission for AMI has declined from 10 to ~5%. The 1-year mortality rate after AMI is ~15%. Mortality is approximately fourfold higher in patients aged >75 years as compared with younger patients.

When patients with prolonged ischemic discomfort at rest are first seen, the working clinical diagnosis is that they are suffering from an acute coronary syndrome (Fig. 286-1). The 12-lead electrocardiogram (ECG) is a pivotal diagnostic and triage tool because it is at the center of the decision pathway for management, permitting distinction of

those patients presenting with ST-segment elevation from those presenting without ST-segment elevation. Circulating cardiac biomarkers of myocardial injury are measured to distinguish unstable angina (UA) from non-ST-segment elevation myocardial infarction (NSTEMI) and to estimate preliminarily the magnitude of myocardial necrosis in an ST-segment elevation myocardial infarction (STEMI). Epidemiologic studies indicate there has been a shift in the pattern of AMI over the past several decades with more patients with NSTEMI than STEMI. This chapter focuses on the evaluation and management of patients with STEMI, while Chap. 286 discusses UA/NSTEMI.

PATHOPHYSIOLOGY: ROLE OF ACUTE PLAQUE RUPTURE/EROSION

STEMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis. Slowly developing, high-grade coronary artery stenoses do not typically precipitate STEMI because of the development of a rich collateral network over time. Instead, STEMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury. This injury is produced or facilitated by factors such as cigarette smoking, hypertension, lipid accumulation, and inflammation. In most cases, STEMI occurs when the surface of an atherosclerotic plaque becomes disrupted either through erosion or rupture (exposing its contents to the blood) and conditions (local or systemic) favor thrombogenesis. Histologic studies indicate that the coronary plaques prone to disruption are those with a rich lipid core and a thin fibrous cap. However, current clinical data have demonstrated that less than 5% of such thin-capped fibroatheromas are a nidus for AMI during long-term follow-up. Other morphologic characteristics associated with rupture-prone plaque include expansive remodeling, neovascularization (angiogenesis), plaque hemorrhage, adventitial inflammation, and a “spotty” pattern of calcification.

A mural thrombus forms at the site of plaque disruption, and the involved coronary artery becomes occluded. After an initial platelet monolayer forms at the site of the disrupted plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, thromboxane A_2 (a potent local vasoconstrictor) is released, further platelet activation occurs, and potential resistance to fibrinolysis develops.

In addition to the generation of thromboxane A_2 , activation of platelets by agonists promotes a conformational change in the glycoprotein IIb/IIIa receptor (Chap. 120). Once converted to its functional state, this receptor develops a high affinity for soluble adhesive proteins (i.e., integrins) such as fibrinogen. Since fibrinogen is a multivalent molecule, it can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation.

The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the disrupted plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin (Chap. 121). Fluid-phase and clot-bound thrombin participate in an autoamplification reaction, leading to further activation of the coagulation cascade. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands (Fig. 286-2).

In rare cases, STEMI may be due to coronary artery occlusion caused by coronary emboli, congenital coronary abnormalities, coronary spasm, or spontaneous coronary artery dissection. The amount of myocardial damage caused by coronary occlusion depends on (1) the territory supplied by the affected vessel, (2) whether or not the vessel becomes totally occluded, (3) the duration of coronary occlusion, (4) the quantity of blood supplied by collateral vessels to the affected tissue, (5) the demand for oxygen of the myocardium whose blood supply has been suddenly limited, (6) endogenous factors that can produce early spontaneous lysis of the occlusive thrombus, and (7) the adequacy of myocardial perfusion in the infarct zone when flow is restored in the occluded epicardial coronary artery.

Patients at increased risk for developing STEMI include those with multiple coronary risk factors and those with UA (Chap. 285). Less

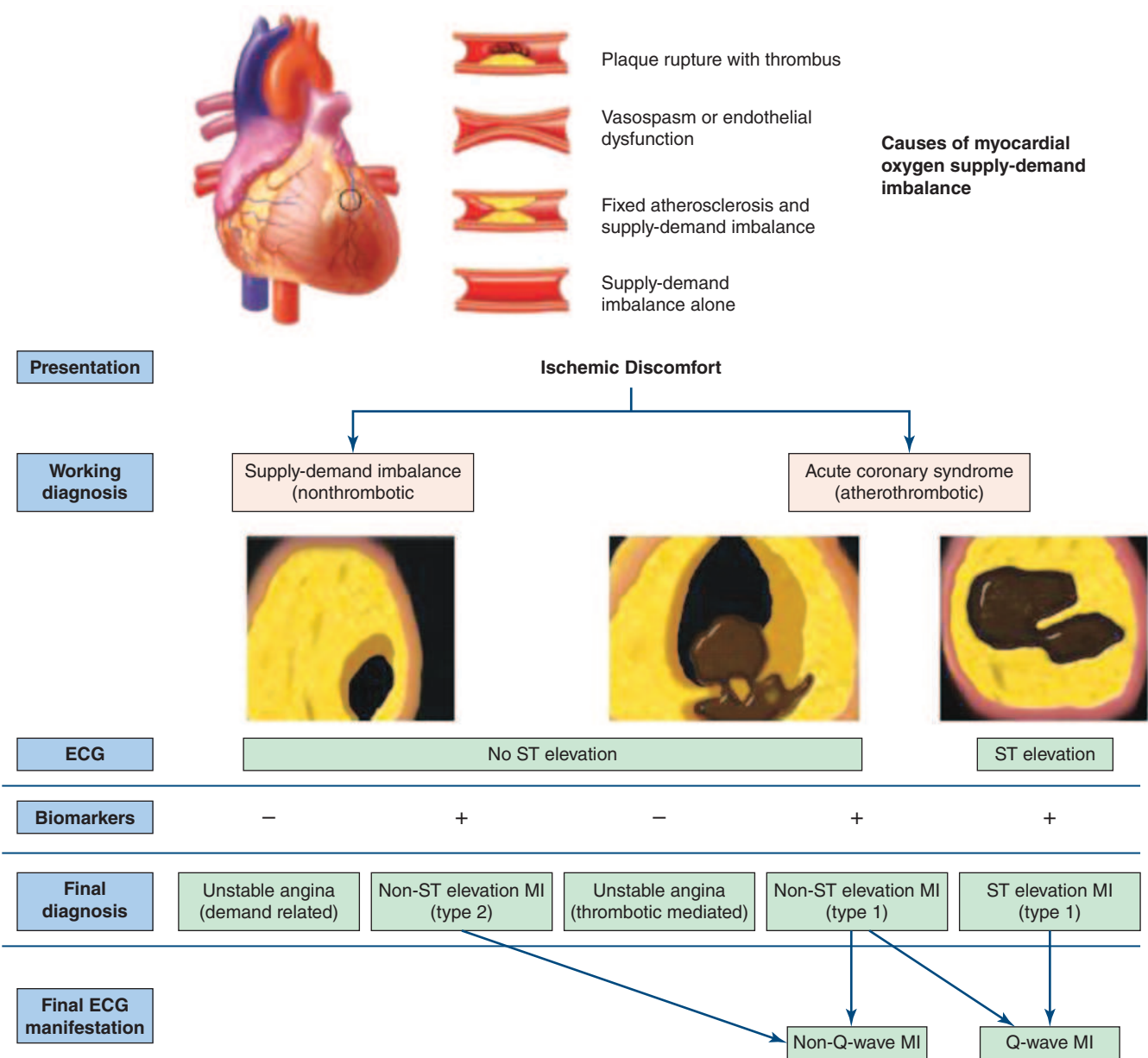


FIGURE 286-1 Acute coronary syndromes. Following disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (right) or subtotally occlusive thrombus (middle). Patients with ischemic discomfort may present with or without ST-segment elevation. Of patients with ST-segment elevation, the majority ultimately develop a Q wave on the electrocardiogram (ECG; Q-wave myocardial infarction [MI]), while a minority do not develop Q waves and, in the past, were said to have sustained a non-Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from either unstable angina or a non-ST-segment elevation MI (NSTEMI), a distinction that is ultimately made based on the presence or absence of a biomarker of myocardial injury such as cardiac troponin detected in the blood. (Reproduced with permission from Hamm Scirica BM, Libby P, Morrow DA: ST-elevation myocardial infarction: Pathophysiology and clinical evolution, in Braunwald's Heart Disease, 12th ed, Libby P et al (eds). New York, Elsevier, 2022, Figure 37-1, pp 636-661.)

common underlying medical conditions predisposing patients to STEMI include hypercoagulability, collagen vascular disease, systemic inflammatory diseases, cocaine abuse, and intracardiac thrombi or masses that produce coronary emboli.

There have been major advances in the management of STEMI with recognition that the “chain of survival” involves a highly integrated system starting with prehospital care and extending to early hospital management so as to provide expeditious implementation of a reperfusion strategy.

CLINICAL PRESENTATION

In up to one-half of cases, a precipitating factor appears to be present before STEMI, such as vigorous physical exercise, emotional stress, or a medical or surgical illness. Although STEMI may commence at any time of the day or night, circadian variations have been reported such that clusters are seen in the morning within a few hours of awakening.

Pain is the most common presenting complaint in patients with STEMI. The pain is deep and visceral; adjectives commonly used to describe it are *heavy*, *squeezing*, and *crushing*; although, occasionally, it is described as stabbing or burning (Chap. 15). It is similar in character to the discomfort of angina pectoris (Chap. 284) but commonly occurs at rest, is usually more severe, and lasts longer. Typically, the pain involves the central portion of the chest and/or the epigastrium, and, on occasion, it radiates to the arms. Less common sites of radiation include the abdomen, back, lower jaw, and neck. The frequent location of the pain beneath the xiphoid and epigastrium and the patients’ denial that they may be suffering a heart attack are chiefly responsible for the common mistaken impression of indigestion. The pain of STEMI may radiate as high as the occipital area but not below the umbilicus. It is often accompanied by sweating, nausea, vomiting, anxiety, and a sense of impending doom. The pain may commence when the patient is at rest, but when it begins during a period of exertion, it does not usually subside with cessation of activity, in contrast to angina pectoris.

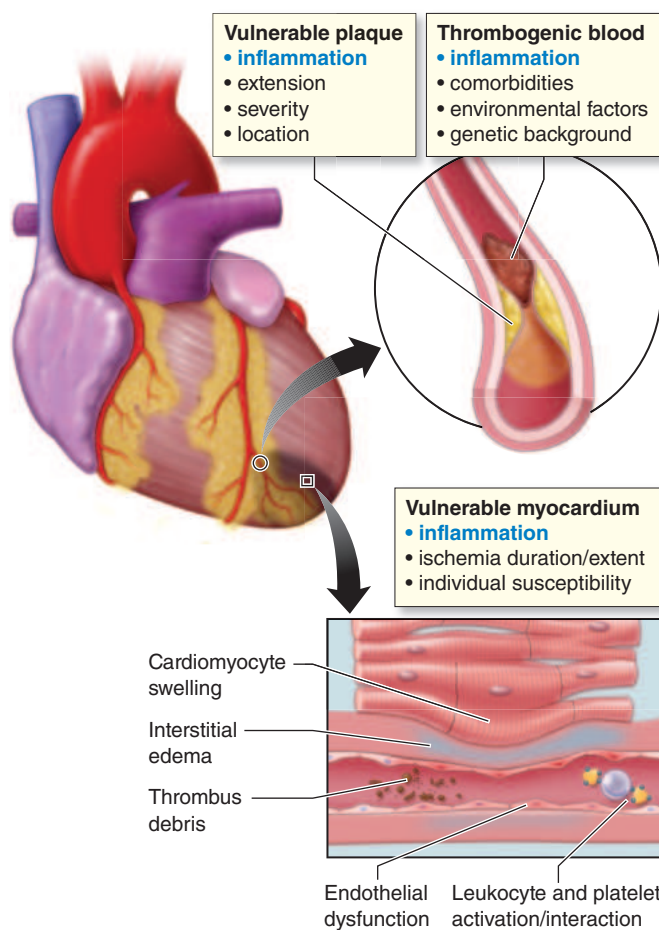


FIGURE 286-2 Critical determinants of myocardial infarction injury. The overlapping of vulnerable plaque and thrombogenic blood are critical determinants for myocardial infarction occurrence and extension. In addition, myocardial vulnerability, which is largely due to coronary microvascular dysfunction, contributes to extension and severity of ischemic injury. In the most severe form (known as no-reflow), structural and functional impairments sustain vascular obstruction. Endothelial dysfunction triggers leukocyte and platelet activation/interaction, whereas thrombotic debris may worsen the obstruction. Furthermore, cardiomyocyte swelling, interstitial edema, and tissue inflammation promote extravascular compression. (Modified from F Montecucco, F Carbone, TH Schindler. Pathophysiology of ST-segment elevation myocardial infarction: Novel mechanisms and treatments. *Eur Heart J* 37:1268, 2016.)

The pain of STEMI can simulate pain from acute pericarditis (Chap. 281), pulmonary embolism (Chap. 290), acute aortic dissection (Chap. 291), costochondritis, and gastrointestinal disorders. These conditions should therefore be considered in the differential diagnosis. Radiation of discomfort to the trapezius is not seen in patients with STEMI and may be a useful distinguishing feature that suggests pericarditis is the correct diagnosis. However, *pain is not uniformly present in patients with STEMI*. The proportion of painless STEMIs is greater in patients with diabetes mellitus, and it increases with age. STEMI may present as sudden-onset breathlessness. Other less common presentations, with or without pain, include sudden loss of consciousness, a confusional state, a sensation of profound weakness, the appearance of an arrhythmia, evidence of peripheral embolism, or merely an unexplained drop in arterial pressure.

PHYSICAL FINDINGS

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and coolness of the extremities occurs commonly. The combination of substernal chest pain persisting for >30 min and diaphoresis strongly suggests STEMI. Although many patients have a normal pulse rate and blood pressure within the first hour of STEMI, patients with anterior infarction may

have manifestations of sympathetic nervous system hyperactivity (tachycardia and/or hypertension), and those with inferior infarction may show evidence of parasympathetic hyperactivity (bradycardia and/or hypotension).

The precordium is usually quiet, and the apical impulse may be difficult to palpate. Other physical signs of ventricular dysfunction include fourth and third heart sounds, decreased intensity of the first heart sound, and paradoxical splitting of the second heart sound (Chap. 246). A transient midsystolic or late systolic apical systolic murmur due to dysfunction of the mitral valve apparatus may be present. A pericardial friction rub may be heard in patients with transmural STEMI at some time in the course of the illness. The carotid pulse is often decreased in volume, reflecting reduced stroke volume. Temperature elevations up to 38°C may be observed during the first week after STEMI.

LABORATORY FINDINGS

STEMI progresses through the following temporal stages: (1) acute (first few hours–7 days), (2) healing (7–28 days), and (3) healed (≥29 days). The myocardium undergoes a series of cellular responses in the infarct zone, beginning with recruitment of polymorphonuclear leukocytes (for removal of dead cells and clearance of extracellular macromolecules) followed by monocytes. Experimental work has now detailed this sequence of accumulation of subpopulations of mononuclear phagocytes with an initial wave of monocytes characterized by high proteolytic and phagocytic capacity and elaboration of proinflammatory cytokines followed by the repair monocytes that release a mediators that stimulate angiogenesis and extracellular matrix production (Fig. 286-3). New microvessels and fibrosis are key constituents of forming granulation tissue, and these processes establish a foundation for myocardial scar formation, ventricular remodeling, and infarct healing. In addition, emerging evidence reveals a role for an “emergency hematopoiesis” that mobilizes leukocyte progenitor cells that ultimately participate in myocardial healing.

When evaluating the results of diagnostic tests for STEMI, the temporal phase of the infarction must be considered. The tests of value in confirming the diagnosis may be divided into four groups: (1) ECG, (2) blood-based cardiac biomarkers, (3) cardiac imaging, and (4) nonspecific indices of tissue necrosis and inflammation.

ELECTROCARDIOGRAM

The electrocardiographic manifestations of STEMI are described in Chap. 247. During the initial stage, total occlusion of an epicardial coronary artery produces ST-segment elevation. Most patients initially presenting with ST-segment elevation ultimately evolve Q waves on the ECG. However, Q waves in the leads overlying the infarct zone may vary in magnitude and appear only transiently, depending on the reperfusion status of the ischemic myocardium and restoration of transmembrane potentials over time. A small proportion of patients initially presenting with ST-segment elevation will not develop Q waves when the obstructing thrombus is not totally occlusive, obstruction is transient, or a rich collateral network is present. Among patients presenting with ischemic discomfort but *without* ST-segment elevation, if a cardiac biomarker of necrosis (see below) is detected, the diagnosis of NSTEMI is ultimately made (Fig. 286-1). A minority of patients who present initially without ST-segment elevation may develop a Q-wave myocardial infarction (MI). Previously, it was believed that transmural MI is present if the ECG demonstrates Q waves or loss of R waves, and nontransmural MI may be present if the ECG shows only transient ST-segment and T-wave changes. However, electrocardiographic-pathologic correlations are far from perfect, and terms such as *Q-wave MI*, *non-Q-wave MI*, *transmural MI*, and *nontransmural MI* have been replaced by STEMI and NSTEMI (Fig. 286-1). Contemporary studies using magnetic resonance imaging (MRI) suggest that the development of a Q wave on the ECG is more dependent on the volume of infarcted tissue rather than the transmural extent of infarction.

CARDIAC BIOMARKERS OF MYOCARDIAL INJURY

Certain proteins, referred to as cardiac biomarkers, are released from necrotic heart muscle after STEMI. The rate of liberation of specific

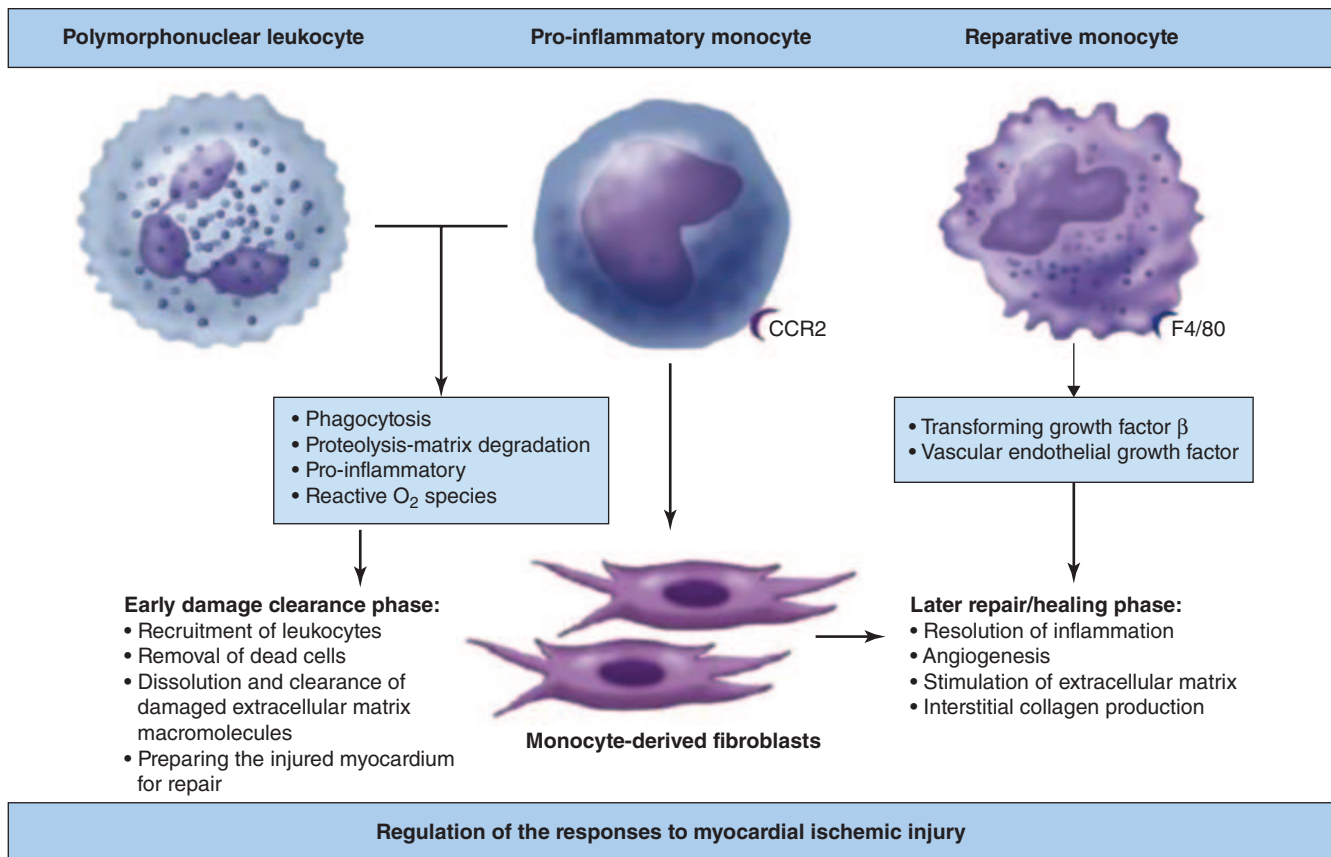


FIGURE 286-3 Phases of myocardial injury and healing. Immediate recruitment of polymorphonuclear leukocytes precedes the accumulation of proinflammatory monocytes (typically bearing the chemokine receptor 2 [CCR2]). These phagocytic cells release the mediators of the early phase response to ischemic injury by clearing dead cells and debris and prompting additional inflammatory cells to enter the injured area. Reparative monocytes stimulate the production of extracellular matrix macromolecules that reinforce the cardiac skeleton during healing as well as microvessel formation characteristic of granulation tissue. Monocyte-derived fibroblasts are capable of interstitial collagen synthesis that reinforces repair of the myocardial skeleton, potentially mitigating expansive remodeling of the infarct and promoting healing with less risk for chronic heart failure. (Reproduced with permission from P Libby et al: *The myocardium: More than just myocytes*. *J Am Coll Cardiol* 74:3137, 2019.)

proteins differs depending on their intracellular location, their molecular weight, and the local blood and lymphatic flow. Cardiac biomarkers become detectable in the peripheral blood once the capacity of the cardiac lymphatics to clear the interstitium of the infarct zone is exceeded and spillover into the venous circulation occurs. The criteria for AMI require a rise and/or fall in cardiac biomarker values with at least one value above the 99th percentile of the upper reference limit for normal individuals.

Cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI) have amino-acid sequences that differ from those of the skeletal muscle forms of these proteins. These differences permitted the development of quantitative assays for cTnT and cTnI using highly specific monoclonal antibodies. cTnT and cTnI may increase after STEMI to levels many times higher than the upper reference limit (set at the 99th percentile of values in a reference population). The measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI when measured with high-sensitivity assays (Fig. 286-4 and Chap. 15). In practical terms, the high-sensitivity troponin assays are of less immediate value in patients with STEMI. Contemporary urgent reperfusion strategies necessitate making a decision (based largely on a combination of clinical and ECG findings) before the results of blood tests have returned from the laboratory. Levels of cTnI and cTnT typically remain elevated for at least 7–10 days after STEMI.

Historically, creatine phosphokinase (CK) and its MB isoenzyme (CK-MB) were used for the diagnosis of AMI. A ratio (relative index) of CK-MB mass to CK activity ≥ 2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CK-MB elevation. It is *not* cost-effective to measure both a cardiac-specific troponin and CK-MB. Because of its more rapid decline after the onset of AMI, CK-MB may be useful for the discrimination of early reinfarction

during the period that cardiac troponin remains elevated following the index event (Fig. 286-3).

While it has long been recognized that the total quantity of protein released correlates with the size of the infarct, the peak protein concentration correlates only weakly with infarct size. Recanalization of a coronary artery occlusion (either spontaneously or by mechanical or pharmacologic means) in the early hours of STEMI causes earlier peaking of biomarker measurements (Fig. 286-4) because of a rapid washout from the interstitium of the infarct zone, quickly overwhelming lymphatic clearance of the proteins.

The *nonspecific reaction* to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain and persists for 3–7 days; the white blood cell count often reaches levels of 12,000–15,000/ μ L. The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks.

CARDIAC IMAGING

Abnormalities of wall motion on *two-dimensional echocardiography* (Chap. 248) are almost universally present in patients with STEMI. Although acute STEMI cannot be distinguished from an old myocardial scar or from acute severe ischemia by echocardiography, the ease and safety of the procedure make its use appealing as a screening tool in the emergency department. When the ECG is not diagnostic of STEMI, early detection of the presence or absence of wall motion abnormalities by echocardiography can aid in management decisions, such as whether the patient should receive reperfusion therapy (e.g., percutaneous coronary intervention [PCI] or fibrinolysis). Echocardiographic estimation of left ventricular (LV) function is useful prognostically; detection of reduced function serves as an indication for

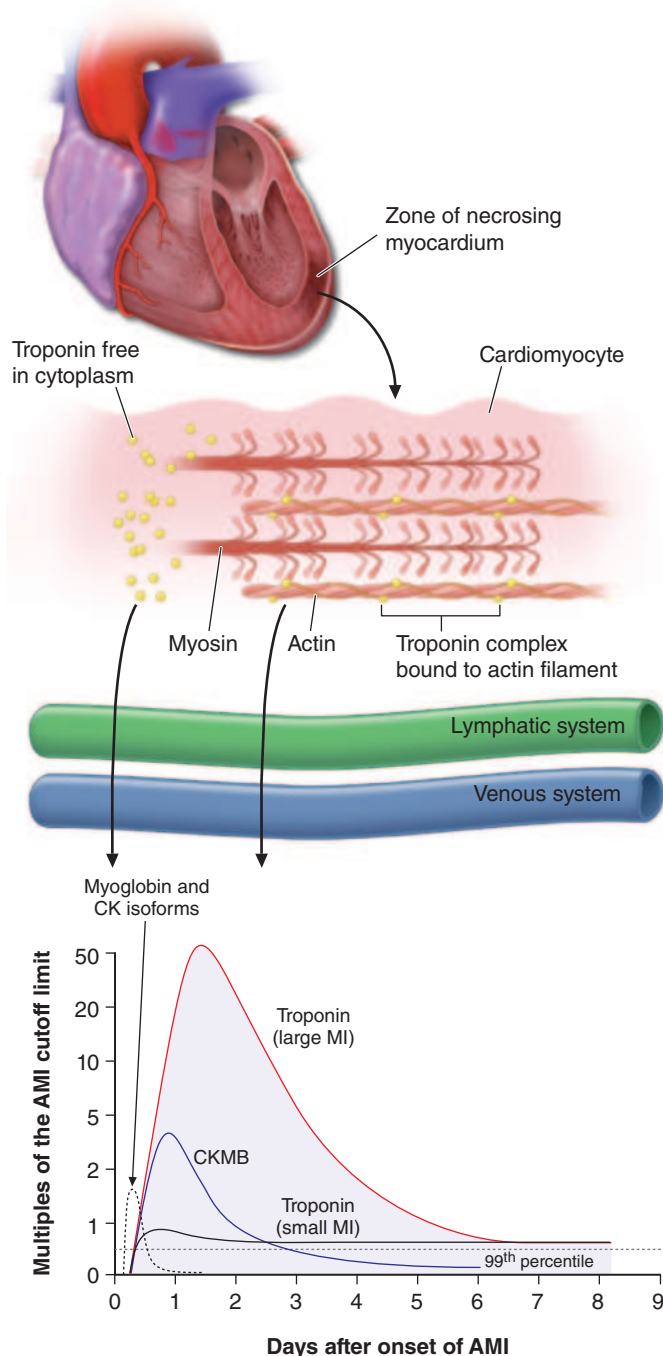


FIGURE 286-4 The zone of necrotic myocardium is shown at the top of the figure, followed in the middle portion of the figure by a diagram of a cardiomyocyte that is in the process of releasing biomarkers. The biomarkers that are released into the interstitium are first cleared by lymphatics followed subsequently by spillover into the venous system. After disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first (*left-most arrow in bottom portion of figure*). Markers such as myoglobin and CK isoforms are rapidly released, and blood levels rise quickly above the cutoff limit; this is then followed by a more protracted release of biomarkers from the disintegrating myofilaments that may continue for several days. Cardiac troponin levels rise to about 20–50 times the upper reference limit (the 99th percentile of values in a reference control group) in patients who have a “classic” acute myocardial infarction (MI) and sustain sufficient myocardial necrosis to result in abnormally elevated levels of the MB fraction of creatine kinase (CK-MB). Clinicians can now diagnose episodes of microinfarction by sensitive assays that detect cardiac troponin elevations above the upper reference limit, even though CK-MB levels may still be in the normal reference range (not shown). CV, coefficient of variation. (Modified from EM Antman: Decision making with cardiac troponin tests. *N Engl J Med* 346:2079, 2002, and; bottom image: Reproduced with permission from AS Jaffe: Biomarkers in acute cardiac disease: The present and the future. *J Am Coll Cardiol* 48:1, 2006.)

therapy with an inhibitor of the renin-angiotensin-aldosterone system. Echocardiography may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of STEMI.

Radionuclide imaging techniques (Chap. 248) are available but rarely used for evaluating patients with suspected STEMI. Myocardial perfusion imaging with [^{99m}Tc]-sestamibi, which is distributed in proportion to myocardial blood flow and concentrated by viable myocardium (Chap. 285), reveals a defect (“cold spot”) in most patients during the first few hours after development of a transmural infarct. However, the technique cannot distinguish acute infarcts from chronic scars and, thus, is not specific for the diagnosis of acute MI.

An Expert Consensus Task Force for the Universal Definition of Myocardial Infarction has provided a comprehensive set of criteria for the definition of MI that integrates the clinical and laboratory findings discussed earlier as well as a classification of MI into five types that reflect the clinical circumstances in which it may occur (Table 286-1).

INITIAL MANAGEMENT

■ PREHOSPITAL CARE

The prognosis in STEMI in the era of primary PCI is largely related to the occurrence of two general classes of complications: (1) electrical complications (arrhythmias) and (2) mechanical complications (“pump failure”). Most out-of-hospital deaths from STEMI result from the sudden development of ventricular fibrillation. The vast majority of deaths due to ventricular fibrillation occur within the first 24 h of the onset of symptoms, and of these, over half occur in the first hour. Therefore, the major elements of prehospital care of patients with suspected STEMI include (1) recognition of symptoms by the patient and prompt seeking of medical attention; (2) rapid deployment of an emergency medical team capable of performing resuscitative maneuvers, including defibrillation; (3) expeditious transportation of the patient to a hospital facility that is continuously staffed by physicians and nurses skilled in managing arrhythmias and providing advanced cardiac life support; and (4) expeditious implementation of reperfusion therapy. The greatest delay usually occurs not during transportation to the hospital but, rather, between the onset of pain and the patient’s decision to call for help. This delay can best be reduced by health care professionals educating the public concerning the significance of chest discomfort and the importance of seeking early medical attention. Regular office visits with patients having a history of, or who are at risk for, ischemic heart disease are important “teachable moments” for clinicians to review the symptoms of AMI and the appropriate action plan.

Increasingly, monitoring and treatment are carried out by trained personnel in the ambulance, further shortening the time between the onset of the infarction and appropriate treatment. In areas remote from PCI centers, fibrinolytic therapy may be administered prehospital. General guidelines for initiation of fibrinolysis in the prehospital setting include the ability to transmit 12-lead ECGs to confirm the diagnosis, the presence in the ambulance of personnel trained in the interpretation of ECGs and management of STEMI, and online medical command and control that can authorize the initiation of treatment in the field.

MANAGEMENT IN THE EMERGENCY DEPARTMENT

In the emergency department, the goals for the management of patients with suspected STEMI include control of cardiac discomfort, rapid identification of patients who are candidates for urgent reperfusion therapy, triage of lower-risk patients to the appropriate location in the hospital, and avoidance of inappropriate discharge of patients with STEMI. Many aspects of the treatment of STEMI are initiated in the emergency department and then continued during the in-hospital phase of management. The overarching goal is to minimize the time from first medical contact to initiation of reperfusion therapy (Fig. 286-5). This may involve transfer from a non-PCI hospital to one

TABLE 286-1 Definitions of Myocardial Injury and Infarction

Criteria for Myocardial Injury

The term *myocardial injury* should be used when there is evidence of elevated cardiac troponin (cTn) levels with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for Acute Myocardial Infarction (types 1, 2, and 3 MI)

The term *acute myocardial infarction* (MI) should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischemia
- New ischemic electrocardiographic (ECG) changes
- Development of pathologic Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs)

Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for *type 2 MI*. Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values became available or abnormal meets criteria for *type 3 MI*.

Criteria for Coronary Procedure–Related MI (types 4 and 5 MI)

Percutaneous coronary intervention (PCI)–related MI is termed *type 4a MI*.

Coronary artery bypass grafting (CABG)–related MI is termed *type 5 MI*.

Coronary procedure–related MI <48 h after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for *type 4a MI* and >10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated preprocedural cTn values, in whom the preprocedural cTn levels are stable (<20% variation) or falling, must meet the criteria for a >5- or >10-fold increase and manifest a change from the baseline value of >20%. In addition, they must have at least one of the following:

- New ischemic ECG changes (this criterion is related to *type 4a MI* only)
- Development of new pathologic Q waves
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow, or distal embolization

Isolated development of new pathologic Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn levels are elevated and rising, but less than the prespecified thresholds for PCI and CABG.

Other types of type 4 MI include *type 4B MI* stent thrombosis and *type 4C MI* restenosis that both meet *type 1 MI* criteria.

Postmortem demonstration of a procedure-related thrombus meets the *type 4a MI* and *type 5 MI* criteria if associated with a stent.

Criteria for Prior or Silent/Unrecognized MI

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of nonischemic causes
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology
- Pathoanatomical findings of a prior MI

Source: Reproduced with permission from K Thygesen et al: Fourth universal definition of myocardial infarction (2018). *Circulation* 138:e618, 2018.

that is PCI capable, with a goal of initiating PCI within 120 min of first medical contact (Fig. 286-5).

Aspirin is essential in the management of patients with suspected STEMI and is effective across the entire spectrum of acute coronary syndromes. Rapid inhibition of cyclooxygenase-1 in platelets followed by a reduction of thromboxane A₂ levels is achieved by buccal absorption of a chewed 160–325-mg tablet in the emergency department. This measure should be followed by daily oral administration of aspirin in a dose of 75–162 mg.

In patients whose arterial oxygen (O₂) saturation is normal, supplemental O₂ is not recommended. However, when hypoxemia is present (O₂ saturation <90%), O₂ should be administered to correct the hypoxemia; the patient should then be reassessed to determine if there is a continued need for such treatment.

CONTROL OF DISCOMFORT

Sublingual *nitroglycerin* can be given safely to most patients with STEMI. Up to three doses of 0.4 mg should be administered at about 5-min intervals in patients with persistent ischemic symptoms. In addition to diminishing or abolishing chest discomfort, nitroglycerin may be capable of both decreasing myocardial O₂ demand (by lowering preload) and increasing myocardial O₂ supply (by dilating infarct-related coronary vessels or collateral vessels and by improving subendocardial perfusion). In patients whose initially favorable response to sublingual nitroglycerin is followed by the return of chest discomfort, particularly if accompanied by other evidence of ongoing ischemia such as further ST-segment or T-wave shifts, the use of intravenous nitroglycerin may be considered. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (<90 mmHg) or in whom there is clinical suspicion of RV infarction (inferior infarction on ECG, elevated jugular venous pressure, clear lungs, and hypotension). Nitrates should not be administered to patients who have taken a phosphodiesterase-5 inhibitor for erectile dysfunction within the preceding 24 h because it may potentiate the hypotensive effects of nitrates. An idiosyncratic reaction to nitrates, consisting of sudden marked hypotension, sometimes occurs but can usually be reversed promptly by the rapid administration of intravenous atropine.

Morphine is a very effective analgesic for the pain associated with STEMI. However, it may reduce sympathetically mediated arteriolar and venous constriction, and the resulting venous pooling may reduce cardiac output and arterial pressure. These hemodynamic disturbances usually respond promptly to elevation of the legs, but in some patients, volume expansion with intravenous saline is required. The patient may experience diaphoresis and nausea, but these events usually pass and are replaced by a feeling of well-being associated with the relief of pain. Morphine also has a vagotonic effect and may cause bradycardia or advanced degrees of heart block, particularly in patients with inferior infarction. These side effects usually respond to atropine (0.5 mg intravenously). Morphine may also slow the gastrointestinal absorption of oral medicines, which may delay the onset of action of orally administered antiplatelet therapy; however, currently available clinical data have not demonstrated an increase in the risk of adverse clinical outcomes as a result of any interaction between morphine and antiplatelet agents. Therefore, it is reasonable to use morphine in patients with STEMI to relieve pain. Morphine is administered by repetitive (every 5 min) intravenous injection of small doses (2–4 mg).

Intravenous *beta blockers* are also useful in mitigating the ischemic pain of STEMI. These drugs control pain effectively in some patients, presumably by diminishing myocardial O₂ demand and hence ischemia. More important, there is evidence that intravenous beta blockers reduce the risks of reinfarction and ventricular fibrillation (see “Beta-Adrenoceptor Blockers” below). A commonly employed regimen is metoprolol, 5 mg every 2–5 min for a total of three doses, provided the patient has a heart rate >60 beats/min, systolic pressure >100 mmHg, a PR interval <0.24 s, and no signs of acute heart failure.

Patient selection is important when considering beta blockers for STEMI. Oral beta blocker therapy should be initiated in the first 24 h for patients who do *not* have any of the following: (1) signs of acute heart failure, (2) evidence of a low-output state, (3) increased risk for cardiogenic shock, or (4) other relative contraindications to beta blockade (bradycardia, PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease). In eligible patients, 15 min after the last intravenous dose, an oral regimen is initiated with 50 mg every 6 h for 48 h, followed by 100 mg every 12 h.

Unlike beta blockers, calcium antagonists are of little value in the acute setting, and there is evidence that short-acting dihydropyridines may be associated with an increased mortality risk.

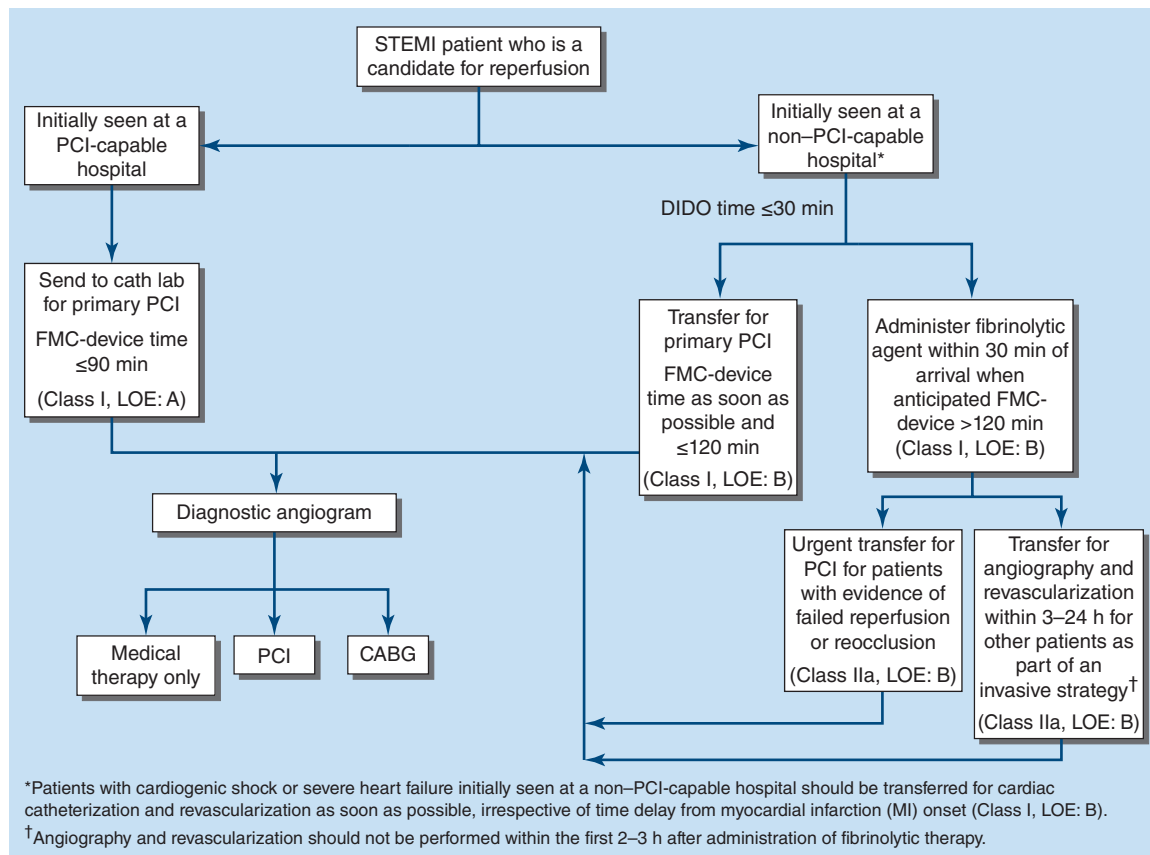


FIGURE 286-5 Reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI). Performance of percutaneous coronary intervention (PCI) is dictated by an anatomically appropriate culprit stenosis. CABG, coronary artery bypass graft; DIDO, door-in–door-out; FMC, first medical contact; LOE, level of evidence. (Reproduced with permission from PT O’Gara: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *Circulation* 127:e362, 2013.)

MANAGEMENT STRATEGIES

The primary tool for screening patients and making triage decisions is the initial 12-lead ECG. When ST-segment elevation meeting the Universal Definition of MI criteria (Table 286-2) is present, a patient should be considered a candidate for *reperfusion therapy* (Figs. 286-1 and 286-5). The process of selecting patients for fibrinolysis versus primary PCI (Chap. 287) is discussed below. In the absence of ST-segment elevation, fibrinolysis is not helpful, and evidence exists suggesting that it may be harmful.

LIMITATION OF INFARCT SIZE

The quantity of myocardium that becomes necrotic as a consequence of a coronary artery occlusion is determined by factors other than just the location of occlusion. While the central zone of the infarct contains necrotic tissue that is irretrievably lost, the fate of the surrounding ischemic myocardium (ischemic penumbra) may be improved by timely restoration of coronary perfusion, reduction of myocardial O₂ demands, prevention of the accumulation of noxious metabolites, and blunting of the impact of mediators of reperfusion injury (e.g., calcium overload and oxygen-derived free radicals). Up to one-third of patients with STEMI may achieve *spontaneous* reperfusion of the infarct-related coronary artery within 24 h and experience improved healing of infarcted tissue.

TABLE 286-2 Electrocardiographic Criteria for ST-Elevation Myocardial Infarction

New ST-elevation at the J-point in 2 contiguous leads with the cut-point:

- In all leads other than leads V_2 – V_3 : ≥ 0.1 mV (1 mm on standard scale)
- In leads V_2 – V_3 :
 - ≥ 0.2 mV (2 mm) in men ≥ 40 years old
 - ≥ 0.25 mV (2.5 mm) in men < 40 years
 - ≥ 0.15 mV (1.5 mm) in women regardless of age

Source: Reproduced from K Thygesen et al: Fourth universal definition of myocardial infarction (2018). *Circulation* 138:e618, 2018.

Reperfusion, either pharmacologically (by fibrinolysis) or by primary PCI, accelerates the opening of infarct-related arteries in those patients in whom spontaneous fibrinolysis ultimately would have occurred and also greatly increases the number of patients in whom restoration of flow in the infarct-related artery is accomplished. Timely restoration of flow in the epicardial infarct-related artery combined with improved perfusion of the downstream zone of infarcted myocardium results in a limitation of infarct size. Protection of the ischemic myocardium by the maintenance of an optimal balance between myocardial O₂ supply and demand through pain control, treatment of heart failure (HF), and minimization of tachycardia and hypertension extends the “window” of time for the salvage of myocardium by reperfusion strategies.

Glucocorticoids and nonsteroidal anti-inflammatory agents, with the exception of aspirin, should be avoided in patients with STEMI. They can impair infarct healing and increase the risk of myocardial rupture, and their use may result in a larger infarct scar. In addition, they can increase coronary vascular resistance, thereby potentially reducing flow to ischemic myocardium.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

(See also Chap. 287) PCI, usually stenting without preceding fibrinolysis, referred to as *primary PCI*, is effective in restoring perfusion in STEMI when carried out on an emergency basis in the first few hours of MI. It has the advantage of being applicable to patients who have contraindications to fibrinolytic therapy (see below) but otherwise are considered appropriate candidates for reperfusion. Primary PCI is more effective than fibrinolysis in opening occluded coronary arteries and, *when performed by experienced teams in dedicated medical centers*, is associated with better short-term and long-term clinical outcomes. Compared with fibrinolysis, primary PCI is preferred unless the time to delivery of the first coronary device is anticipated to be longer than 120 min. Primary PCI is also preferred when the diagnosis is in doubt, cardiogenic shock is present, bleeding risk is high, or symptoms have

been present for longer than 2–3 h, at which time the clot is less easily lysed by fibrinolytic drugs. Contemporary studies (PRAMI, CvLPRIT, COMPLETE) provide evidence that, in patients with STEMI without shock, performing PCI on nonculprit coronary vessels, either during the index procedure or within 45 days, results in a lower rate of cardiovascular events and a lower need for subsequent ischemia-driven revascularization. In contrast, among patients with cardiogenic shock, routine PCI of nonculprit arteries during the initial primary PCI is contraindicated due to an increase in the rate of death or severe renal failure compared with culprit-only PCI.

■ FIBRINOLYSIS

If timely primary PCI is not available and no contraindications are present (see below), fibrinolytic therapy should ideally be initiated within 30 min of presentation (i.e., door-to-needle time ≤ 30 min). The principal goal of fibrinolysis is prompt restoration of full coronary arterial patency. The fibrinolytic agents tissue plasminogen activator (tPA), streptokinase, tenecteplase (TNK), and reteplase (rPA) have been approved by the U.S. Food and Drug Administration for intravenous use in patients with STEMI. These drugs all act by promoting the conversion of plasminogen to plasmin, which subsequently lyses fibrin thrombi. Although considerable emphasis was first placed on a distinction between more fibrin-specific agents, such as tPA, and non-fibrin-specific agents, such as streptokinase, it is now recognized that these differences are only relative, as some degree of systemic fibrinolysis occurs with the former agents. TNK and rPA are referred to as *bolus fibrinolytics* since their administration does not require a prolonged intravenous infusion.

When assessed angiographically, flow in the culprit coronary artery is described by a simple qualitative scale called the *Thrombolysis in Myocardial Infarction (TIMI) grading system*: grade 0 indicates complete occlusion of the infarct-related artery; grade 1 indicates some penetration of the contrast material beyond the point of obstruction, but without perfusion of the distal coronary bed; grade 2 indicates perfusion of the entire infarct vessel into the distal bed, but with flow that is delayed compared with that of a normal artery; and grade 3 indicates full perfusion of the infarct vessel with normal flow. The latter is the goal of reperfusion therapy, because full perfusion of the infarct-related coronary artery yields far better results in terms of limiting infarct size, maintenance of LV function, and reduction of both short- and long-term mortality rates.

tPA and the other relatively fibrin-specific plasminogen activators, rPA and TNK, are more effective than streptokinase at restoring full perfusion—i.e., TIMI grade 3 coronary flow—and have a small edge in improving survival as well. The recommended regimen of tPA consists of a 15-mg bolus followed by 50 mg intravenously over the first 30 min, followed by 35 mg over the next 60 min. Streptokinase is administered as 1.5 million units (MU) intravenously over 1 h. rPA is administered in a double-bolus regimen consisting of a 10-MU bolus given over 2–3 min, followed by a second 10-MU bolus 30 min later. TNK is given as a single weight-based intravenous bolus of 0.53 mg/kg over 10 s. In addition to the fibrinolytic agents discussed earlier, pharmacologic reperfusion typically involves adjunctive antiplatelet and antithrombotic drugs, as discussed subsequently.

Clear contraindications to the use of fibrinolytic agents include a history of cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (a reliably determined systolic arterial pressure >180 mmHg and/or a diastolic pressure >110 mmHg) at any time during the acute presentation, suspicion of aortic dissection, and active internal bleeding (excluding menses). While advanced age is associated with an increase in hemorrhagic complications, the benefit of fibrinolytic therapy in the elderly appears to justify its use if no other contraindications are present, the amount of myocardium in jeopardy appears to be substantial, and timely access to primary PCI is not available.

Relative contraindications to fibrinolytic therapy, which require assessment of the risk-to-benefit ratio, include current use of anti-coagulants (international normalized ratio ≥ 2), a recent (<2 weeks)

invasive or surgical procedure or prolonged (>10 min) cardiopulmonary resuscitation, known bleeding diathesis, pregnancy, a hemorrhagic ophthalmic condition (e.g., hemorrhagic diabetic retinopathy), active peptic ulcer disease, and a history of severe hypertension that is currently adequately controlled. Because of the risk of an allergic reaction, patients should not receive streptokinase if that agent had been received within the preceding 5 days to 2 years.

Allergic reactions to streptokinase occur in $\sim 2\%$ of patients who receive it. While a minor degree of hypotension occurs in 4–10% of patients given this agent, marked hypotension occurs, although rarely, in association with severe allergic reactions.

Hemorrhage is the most frequent and potentially the most serious complication. Because bleeding episodes that require transfusion are more common when patients require invasive procedures, unnecessary venous or arterial interventions should be avoided in patients receiving fibrinolytic agents. Hemorrhagic stroke is the most serious complication and occurs in ~ 0.5 – 0.9% of patients being treated with these agents. This rate increases with advancing age, with patients >70 years experiencing roughly twice the rate of intracranial hemorrhage as those <65 years. Large-scale trials have suggested that the rate of intracranial hemorrhage with tPA or rPA is slightly higher than with streptokinase.

■ INTEGRATED REPERFUSION STRATEGY

Timely performance of PCI is the preferred reperfusion strategy in the management of STEMI. Prior approaches that segregated the pharmacologic and catheter-based approaches to reperfusion have now been replaced with an integrated approach to triage and transfer STEMI patients to receive PCI (Fig. 286-5). To achieve the degree of integration required to care for a patient with STEMI, all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of emergency medical services and hospital-based activities.

In patients who have been treated with a fibrinolytic, urgent coronary angiography should be performed if there is evidence of either (1) failure of reperfusion (persistent chest pain and ST-segment elevation >90 min), in which case a *rescue PCI* should be considered; or (2) coronary artery reocclusion (re-elevation of ST segments and/or recurrent chest pain) or the development of recurrent ischemia. Moreover, transfer to a PCI-capable center is recommended in all patients immediately after fibrinolysis with intent for angiography and PCI of the infarct-related artery, if indicated, between 3 and 24 h after successful fibrinolysis. Coronary artery bypass surgery should be reserved for patients whose coronary anatomy is unsuited to PCI but in whom revascularization appears to be advisable because of extensive jeopardized myocardium or recurrent ischemia.

HOSPITAL PHASE MANAGEMENT

■ CARDIAC INTENSIVE CARE UNITS

These units, previously described as coronary care units, are routinely equipped with continuous monitoring of the cardiac rhythm of each patient and hemodynamic monitoring in selected patients. Equally important is the organization of a highly trained team of nurses who can recognize arrhythmias and perform cardiac resuscitation, including electroshock, when necessary. The availability of electrocardiographic monitoring and trained personnel outside the coronary care unit has made it possible to admit lower-risk patients (e.g., those not hemodynamically compromised and without active arrhythmias) to “intermediate care units.” However, it remains reasonable to admit patients with STEMI to a cardiac intensive care unit when high-risk features are present (e.g., hemodynamic or electrical instability) or when suitably equipped and staffed intermediate care units are not available.

The duration of stay in the coronary care unit is dictated by the ongoing need for intensive care. In general, patients with STEMI who remain at low risk (no persistent chest discomfort, HF, hypotension, or cardiac arrhythmias) may be safely transferred out of the coronary care unit within 24–48 h.

Activity Factors that increase the work of the heart during the initial hours of infarction may increase the size of the infarct. Therefore, patients with STEMI should generally be kept at bed rest for the first 6–12 h. However, in the absence of complications, patients should be encouraged, under supervision, to resume an upright posture by dangling their feet over the side of the bed and sitting in a chair within the first 24 h. This practice is psychologically beneficial and usually results in a reduction in the pulmonary capillary wedge pressure. In the absence of hypotension and other complications, patients typically are ambulating with increasing duration, anticipating that they may be discharged after 3–5 days.

Diet Because of the risk of emesis and aspiration soon after STEMI, patients should receive either nothing or only clear liquids by mouth for the first 4–12 h. The typical diet after AMI should provide $\leq 30\%$ of total calories as fat and have a cholesterol content of ≤ 300 mg/d. Complex carbohydrates should make up 50–55% of total calories. Portions should not be unusually large, and the menu should be enriched with foods that are high in potassium, magnesium, and fiber, but low in sodium. Diabetes mellitus and hypertriglyceridemia are managed by restriction of concentrated sweets in the diet.

PHARMACOTHERAPY

■ ANTITHROMBOTIC AGENTS

The use of antiplatelet and anticoagulant therapy during the initial phase of STEMI is based on extensive laboratory and clinical evidence that thrombosis plays an important role in the pathogenesis of this condition. The primary goal of treatment with antiplatelet and anticoagulant agents is to maintain patency of the infarct-related artery, in conjunction with reperfusion strategies. A secondary goal is to reduce the patient's tendency to thrombosis and, thus, the likelihood of mural thrombus formation or deep-venous thrombosis. The degree to which antiplatelet and anticoagulant therapy achieves these goals partly determines how effectively it reduces the risk of mortality from STEMI.

As noted previously (see “Management in the Emergency Department” earlier), aspirin is the standard antiplatelet agent for patients with STEMI. The most compelling evidence for the benefits of antiplatelet therapy (mainly with aspirin) in STEMI is found in the comprehensive overview by the Antiplatelet Trialists' Collaboration. Data from nearly 20,000 patients with MI enrolled in 15 randomized trials were pooled and revealed a relative reduction of 27% in the mortality rate, from 14.2% in control patients to 10.4% in patients receiving antiplatelet agents.

Inhibitors of the P2Y₁₂ ADP receptor prevent activation and aggregation of platelets. The addition of the P2Y₁₂ inhibitor clopidogrel to background treatment with aspirin to STEMI patients reduces the risk of clinical events (death, reinfarction, stroke) and, in patients receiving fibrinolytic therapy, has been shown to prevent reocclusion of a successfully reperfused infarct artery. Third-generation oral P2Y₁₂ ADP receptor antagonists, such as prasugrel and ticagrelor, are more effective than clopidogrel in preventing ischemic complications in STEMI patients undergoing PCI but are associated with an increased risk of bleeding. Glycoprotein IIb/IIIa receptor inhibitors may be used when thrombotic complications occur during PCI.

The anticoagulant agent most commonly used in clinical practice is unfractionated heparin (UFH). Use of UFH is recommended in patients with STEMI undergoing primary PCI. In addition, the available data suggest that when UFH is added to a regimen of aspirin and a non-fibrin-specific thrombolytic agent such as streptokinase, additional mortality benefit occurs (about 5 lives saved per 1000 patients treated). The immediate administration of intravenous UFH, in addition to a regimen of aspirin and relatively fibrin-specific fibrinolytic agents (tPA, rPA, or TNK), helps to maintain patency of the infarct-related artery. This effect is achieved at the cost of a small increased risk of bleeding. The recommended dose of UFH is an initial bolus of 60 U/kg (maximum 4000 U) followed by an initial infusion of 12 U/kg per h (maximum 1000 U/h). The activated partial thromboplastin time during maintenance therapy should be 1.5–2 times the control value.

Alternatives to UFH for anticoagulation of patients with STEMI are the low-molecular-weight heparin (LMWH) preparations, a synthetic version of the critical pentasaccharide sequence (fondaparinux), and the direct antithrombin bivalirudin. Advantages of LMWHs include high bioavailability permitting administration subcutaneously, reliable anticoagulation without monitoring, and greater anti-Xa:IIa activity. Enoxaparin has been shown to reduce significantly the composite endpoints of death/nonfatal reinfarction and death/nonfatal reinfarction/urgent revascularization compared with UFH in STEMI patients who receive fibrinolysis. Treatment with enoxaparin is associated with higher rates of serious bleeding, but net clinical benefit—a composite endpoint that combines efficacy and safety—still favors enoxaparin over UFH. Interpretation of the data on fondaparinux is difficult because of the complex nature of the pivotal clinical trial evaluating it in STEMI (OASIS-6). Fondaparinux appears superior to placebo in STEMI patients not receiving reperfusion therapy, but its relative efficacy and safety compared with UFH are less certain. Owing to the risk of catheter thrombosis, fondaparinux should not be used alone at the time of coronary angiography and PCI but should be combined with another anticoagulant with antithrombin activity such as UFH or bivalirudin. Trials of bivalirudin used an open-label design to evaluate its efficacy and safety compared with UFH plus a glycoprotein IIb/IIIa inhibitor. Bivalirudin was associated with a lower rate of bleeding, largely driven by reductions in vascular access site hematomas ≥ 5 cm or the administration of blood transfusions. Bivalirudin is an alternative to UFH in patients undergoing primary PCI.

Patients with an anterior location of the infarction, severe LV dysfunction, HF, a history of embolism, or two-dimensional echocardiographic evidence of mural thrombus are at increased risk of systemic or pulmonary thromboembolism. Patients with suspected mural thrombus should receive full therapeutic levels of anticoagulant therapy (LMWH or UFH) while hospitalized, followed by at least 3 months of oral anticoagulant therapy. It is reasonable to consider extended oral anticoagulant therapy (i.e., up to 3 months after presentation with STEMI) in patients with a high risk of developing systemic thromboembolism because of a large area of akinetic myocardium.

■ BETA-ADRENOCEPTOR BLOCKERS

The benefits of beta blockers in patients with STEMI can be divided into those that occur immediately when the drug is given acutely and those that accrue over the long term when the drug is given for secondary prevention after an infarction. Acute intravenous beta blockade, although no longer routinely recommended because of the risk of precipitating heart failure, improves the myocardial O₂ supply-demand relationship, decreases pain, reduces infarct size, and decreases the incidence of serious ventricular arrhythmias. In patients who undergo fibrinolysis soon after the onset of chest pain, no incremental reduction in mortality rate is seen with beta blockers, but recurrent ischemia and reinfarction are reduced.

Oral beta-blocker therapy after STEMI is useful for most patients (including those treated with an angiotensin-converting enzyme [ACE] inhibitor) except those in whom it is specifically contraindicated (patients with HF or severely compromised LV function, heart block, orthostatic hypotension, or a history of asthma) and perhaps those whose excellent long-term prognosis (defined as an expected mortality rate of $<1\%$ per year, patients <55 years, no previous MI, with normal ventricular function, no complex ventricular ectopy, and no angina) markedly diminishes any potential benefit.

■ INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

ACE inhibitors reduce the mortality rate after STEMI, and the mortality benefits are additive to those achieved with aspirin and beta blockers. The maximum benefit is seen in high-risk patients (those who have an anterior infarction, a prior infarction, and/or globally depressed LV function), but evidence suggests that a short-term benefit occurs when ACE inhibitors are prescribed unselectively to all hemodynamically stable patients with STEMI (i.e., those with a systolic pressure >100 mmHg). The mechanism involves a reduction in ventricular remodeling after infarction (see

“Ventricular Dysfunction” later) with a subsequent reduction in the risk of HF. The rate of recurrent infarction may also be lower in patients treated chronically with ACE inhibitors after infarction.

ACE inhibitors should be continued indefinitely in patients who have clinically evident HF, in patients in whom an imaging study shows a reduction in global LV function or a large regional wall motion abnormality, or in those who are hypertensive.

Angiotensin receptor blockers (ARBs) should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiologic signs of HF. Long-term mineralocorticoid receptor inhibition (spironolactone, eplerenone) should be prescribed for STEMI patients who are already receiving therapeutic doses of an ACE inhibitor, have an LV ejection fraction $\leq 40\%$, and have either symptomatic HF or diabetes mellitus and do not have significant renal dysfunction (creatinine ≥ 2.5 mg/dL in men and ≥ 2.0 mg/dL in women) or hyperkalemia (potassium ≥ 5.0 mEq/L).

Although angiotensin receptor–neprilysin inhibition with sacubitril/valsartan is more effective than ACE inhibitor therapy in patients with symptomatic HF with a reduced ejection fraction, sacubitril/valsartan was not more effective than an ACE inhibitor in preventing the development of incident HF in patients early post-MI.

■ OTHER AGENTS

Favorable effects on the ischemic process and ventricular remodeling (see below) previously led many physicians to routinely use *intravenous nitroglycerin* (5–10 μ g/min initial dose and up to 200 μ g/min as long as hemodynamic stability is maintained) for the first 24–48 h after the onset of infarction. However, a subsequent large, randomized trial demonstrated no benefit of intravenous nitroglycerin with respect to major outcomes in patients with STEMI. Use of intravenous nitroglycerin may be considered in patients with STEMI who have persistent hypertension, HF, or ongoing ischemia.

Results of multiple trials of different calcium antagonists have failed to establish a role for these agents in the treatment of most patients with STEMI. Therefore, the routine use of calcium antagonists cannot be recommended. Targeted control of blood glucose in diabetic patients with STEMI has been shown to reduce the mortality rate. Serum magnesium should be measured in all patients on admission, and any demonstrated deficits should be corrected to minimize the risk of arrhythmias.

COMPLICATIONS AND THEIR MANAGEMENT

Recognition and management of the complications of STEMI are essential elements of the care of this patient population (Table 286-3).

■ VENTRICULAR DYSFUNCTION

After STEMI, the left ventricle undergoes a series of changes in shape, size, and thickness in both the infarcted and noninfarcted segments. This process is referred to as *ventricular remodeling* and generally precedes the development of clinically evident HF in the months to years after infarction. Soon after STEMI, the left ventricle begins to dilate. Acutely, this results from expansion of the infarct, i.e., slippage of muscle bundles, disruption of normal myocardial cells, and tissue loss within the necrotic zone, resulting in disproportionate thinning and elongation of the infarct zone. Later, lengthening of the noninfarcted segments occurs as well. The overall chamber enlargement that occurs is related to the size and location of the infarct, with greater dilation following infarction of the anterior wall and apex of the left ventricle and causing more marked hemodynamic impairment, more frequent HF, and a poorer prognosis. Progressive dilation and its clinical consequences may be ameliorated by therapy with ACE inhibitors. In patients with an ejection fraction $<40\%$, regardless of whether or not HF is present, ACE inhibitors or ARBs, and eventually a beta blocker, should be prescribed (see “Inhibition of the Renin-Angiotensin-Aldosterone System” earlier).

■ HEMODYNAMIC ASSESSMENT

Pump failure is now the primary cause of in-hospital death from STEMI. The extent of infarction correlates well with the degree of pump failure and with mortality, both early (within 10 days of infarction) and later. The most common clinical signs are pulmonary rales and an S_3 gallop sound. Pulmonary congestion is also frequently seen on the chest roentgenogram. Elevated LV filling pressure and elevated pulmonary artery pressure are the characteristic hemodynamic findings, but these findings may result from a reduction of ventricular compliance (diastolic failure) and/or a reduction of stroke volume with secondary cardiac dilation (systolic failure) (Chap. 264).

A classification originally proposed by Killip divides patients into four groups: class I, no signs of pulmonary or venous congestion; class II, moderate HF as evidenced by rales at the lung bases, S_3 gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion; class III, severe HF and pulmonary edema; and class IV, shock with systolic pressure <90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion, and oliguria. When this classification was established in 1967, the expected hospital mortality rate of patients in these classes was as follows: class I, 0–5%; class II, 10–20%; class III, 35–45%; and class IV, 85–95%. With advances in management, the mortality rate in each class has fallen, perhaps by as much as

TABLE 286-3 Mechanical Complications of ST-Elevation Myocardial Infarction

CHARACTERISTIC	VENTRICULAR SEPTAL RUPTURE	RUPTURE OF THE VENTRICULAR FREE WALL	PAPILLARY MUSCLE RUPTURE
Incidence	0.2–3% without reperfusion therapy, 0.2–0.34% with fibrinolytic therapy, 3.9% in patients with cardiogenic shock	Approximately 0.3–1%; fibrinolytic therapy does not reduce risk; primary PCI seems to reduce risk	Approximately 0.1–1% (posteromedial more frequent than anterolateral papillary muscle rupture)
Time course	Bimodal peak; within 24 h and 3–5 days; range, 1–14 days	Bimodal peak; within 24 h and 3–5 days; range, 1–14 days	Bimodal peak; within 24 h and 3–5 days; range, 1–14 days
Clinical manifestations	Chest pain, shortness of breath, hypotension	Anginal, pleuritic, or pericardial chest pain; syncope; hypotension; restlessness; sudden death	Abrupt onset of shortness of breath and pulmonary edema; hypotension
Physical findings	Harsh holosystolic murmur, thrill, S_3 , accentuated S_2 , pulmonary edema, RV and LV failure, cardiogenic shock	Jugular venous distention (29% of patients), pulsus paradoxus (47%), electromechanical dissociation, cardiogenic shock	A soft murmur in some cases, no thrill, variable signs of RV overload, severe pulmonary edema, cardiogenic shock
Echocardiographic findings	Ventricular septal rupture, left-to-right shunt on color flow Doppler echocardiography through the ventricular septum, pattern of RV overload	>5 mm pericardial effusion not visualized in all cases; layered, high-acoustic echoes within the pericardium (blood clot); direct visualization of tear; signs of tamponade	Hypercontractile LV, torn papillary muscle or chordae tendineae, flail leaflet, severe mitral regurgitation on color flow Doppler echocardiography
Right-heart catheterization	Increase in oxygen saturation from the RA to RV, large v waves	Ventriculography insensitive, classic signs of tamponade not always present (equalization of diastolic pressures in the cardiac chambers)	No increase in oxygen saturation from the RA to RV, large v waves, very high PCWP

Abbreviations: LV, left ventricle; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle.

Source: Reproduced with permission from Bohula EA, Morrow DA: ST-elevation myocardial infarction: Management, in Braunwald's Heart Disease, 12th ed, Libby P et al (eds). New York, Elsevier, 2022, pp 662–713.

one-third to one-half. However, the mortality rate for patients with cardiogenic shock (class IV) has plateaued without additional improvement for the past 25 years.

Hemodynamic evidence of abnormal global LV function appears when contraction is seriously impaired in 20–25% of the left ventricle. Infarction of $\geq 40\%$ of the left ventricle usually results in cardiogenic shock (**Chap. 316**). Positioning of a balloon flotation (Swan-Ganz) catheter in the pulmonary artery permits monitoring of LV filling pressure as well as estimation of the cardiac output; this technique may be useful in patients who exhibit hypotension and/or clinical evidence of HF. With the addition of intraarterial pressure monitoring, systemic vascular resistance can be calculated as a guide to adjusting vasopressor and vasodilator therapy. Some patients with STEMI have markedly elevated LV filling pressures (>22 mmHg) and normal cardiac indices ($2.6\text{--}3.6$ L/[min/m²]), while others have relatively low LV filling pressures (<15 mmHg) and reduced cardiac indices. The former patients usually benefit from diuresis, while the latter may respond to volume expansion.

■ HYPOVOLEMIA

This is an easily corrected condition that may contribute to the hypotension and vascular collapse associated with STEMI in some patients. It may be secondary to previous diuretic use, to reduced fluid intake during the early stages of the illness, and/or to vomiting associated with pain or medications. Consequently, hypovolemia should be identified and corrected in patients with STEMI and hypotension by cautious fluid administration during continuous monitoring of oxygenation before more vigorous forms of therapy are begun. Eventually, the cardiac output plateaus, and further increases in LV filling pressure only increase congestive symptoms and decrease systemic oxygenation without raising arterial pressure.

TREATMENT

Heart Failure

The management of HF in association with STEMI is similar to that of acute HF secondary to other forms of heart disease (avoidance of hypoxemia, diuresis, afterload reduction, inotropic support) (**Chap. 264**), except that the benefits of digitalis administration to patients with STEMI are unimpressive. By contrast, diuretic agents are extremely effective, as they diminish pulmonary congestion in the presence of systolic and/or diastolic HF. LV filling pressure falls, and orthopnea and dyspnea improve after the intravenous administration of furosemide or other loop diuretics. Nitrates in various forms may be used to decrease preload and congestive symptoms. Oral isosorbide dinitrate, topical nitroglycerin ointment, and intravenous nitroglycerin all have the advantage over a diuretic of lowering preload through venodilation without decreasing the total plasma volume. In addition, nitrates may improve ventricular compliance if ischemia is present, as ischemia causes an elevation of LV filling pressure. Vasodilators must be used with caution to prevent serious hypotension. As noted earlier, ACE inhibitors are an ideal class of drugs for management of ventricular dysfunction after STEMI, especially for the long term. (See “Inhibition of the Renin-Angiotensin-Aldosterone System” earlier.)

■ CARDIOGENIC SHOCK

Prompt reperfusion, efforts to reduce infarct size, and treatment of ongoing ischemia and other complications of MI appear to have reduced the incidence of cardiogenic shock from 20 to $\sim 7\%$. Among those who exhibit cardiogenic shock, only 10% of patients with this condition present with it on admission, while 90% develop it during hospitalization. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease with evidence of “piece-meal” necrosis extending outward from the original infarct zone. **The evaluation and management of cardiogenic shock after STEMI are discussed in detail in Chap. 316.**

■ RIGHT VENTRICULAR INFARCTION

Approximately one-third of patients with inferior infarction demonstrate at least a minor degree of RV necrosis. An occasional patient with inferoposterior LV infarction also has extensive RV infarction, and rare patients present with infarction limited primarily to the RV. Clinically significant RV infarction causes signs of severe RV failure (jugular venous distention, Kussmaul’s sign, hepatomegaly [**Chap. 246**]) with or without hypotension. ST-segment elevations of right-sided precordial ECG leads, particularly lead V₄R, are frequently present in the first 24 h in patients with RV infarction. Two-dimensional echocardiography is helpful in determining the degree of RV dysfunction. Catheterization of the right side of the heart often reveals a distinctive hemodynamic pattern resembling constrictive pericarditis (steep right atrial “y” descent and an early diastolic dip and plateau in RV waveforms) (**Chap. 281**). Therapy consists of volume expansion to maintain adequate RV preload and efforts to improve LV performance with attendant reduction in pulmonary capillary wedge and pulmonary arterial pressures.

■ ARRHYTHMIAS

(See also **Chaps. 251 and 253**) The incidence of arrhythmias after STEMI is higher in patients seen early after the onset of symptoms. The mechanisms responsible for infarction-related arrhythmias include autonomic nervous system imbalance, electrolyte disturbances, ischemia, and slowed conduction in zones of ischemic myocardium. An arrhythmia can usually be managed successfully if trained personnel and appropriate equipment are available when it develops. Since most deaths from arrhythmia occur during the first few hours after infarction, the effectiveness of treatment relates directly to the speed with which patients come under medical observation. The prompt management of arrhythmias constitutes a significant advance in the treatment of STEMI.

Ventricular Premature Beats Infrequent, sporadic ventricular premature depolarizations occur in almost all patients with STEMI and do not require therapy. Whereas in the distant past, frequent, multifocal, or early diastolic ventricular extrasystoles (so-called warning arrhythmias) were routinely treated with antiarrhythmic drugs to reduce the risk of development of ventricular tachycardia and ventricular fibrillation, pharmacologic therapy is now reserved for patients with sustained ventricular arrhythmias. Prophylactic antiarrhythmic therapy (either intravenous lidocaine early or oral agents later) is contraindicated for ventricular premature beats in the absence of clinically important ventricular tachyarrhythmias because such therapy may increase the mortality rate. Beta-adrenoceptor blocking agents are effective in abolishing ventricular ectopic activity in patients with STEMI and in the prevention of ventricular fibrillation. As described earlier (see “Beta-Adrenoceptor Blockers”), they should be used routinely in patients without contraindications. In addition, hypokalemia and hypomagnesemia are risk factors for ventricular fibrillation in patients with STEMI; to reduce the risk, the serum potassium concentration should be adjusted to ~ 4.5 mmol/L and magnesium to ~ 2.0 mmol/L.

Ventricular Tachycardia and Fibrillation Sustained ventricular tachycardia that is well tolerated hemodynamically should be treated with an intravenous regimen of amiodarone (bolus of 150 mg over 10 min, followed by infusion of 1.0 mg/min for 6 h and then 0.5 mg/min). A less desirable but alternative regimen is procainamide (bolus of 15 mg/kg over 20–30 min; infusion of 1–4 mg/min). If ventricular tachycardia does not stop promptly, electrical cardioversion should be used (**Chap. 253**). An unsynchronized discharge of 200 J (biphasic waveform) is used immediately in patients with ventricular fibrillation or when ventricular tachycardia causes hemodynamic deterioration. Ventricular tachycardia or fibrillation that is refractory to electroshock may be more responsive after the patient is treated with amiodarone (150-mg bolus).

Ventricular arrhythmias, including the unusual form of ventricular tachycardia known as *torsades des pointes* (**Chaps. 259 and 261**), may occur in patients with STEMI as a consequence of ongoing ischemia or

other concurrent problems (e.g., hypoxia, hypokalemia, or other electrolyte disturbances) or of the toxic effects of a QT-prolonging agent being administered to the patient. A search for such secondary causes should always be undertaken.

Although the in-hospital mortality rate is increased, the long-term survival is excellent in patients who survive to hospital discharge after primary ventricular fibrillation; i.e., ventricular fibrillation that is a primary response to acute ischemia that occurs during the first 48 h and is not associated with predisposing factors such as HF, shock, bundle branch block, or ventricular aneurysm. This natural history is in sharp contrast to the poor prognosis for patients who develop ventricular fibrillation secondary to severe pump failure. For patients who develop ventricular tachycardia or ventricular fibrillation late in their hospital course (i.e., after the first 48 h), the mortality rate is increased both in-hospital and during long-term follow-up. Such patients should be considered for implantation of a cardioverter-defibrillator (ICD) (Chap. 259). A more challenging issue is the prevention of sudden cardiac death from ventricular fibrillation late after STEMI in patients who have not exhibited sustained ventricular tachyarrhythmias during their index hospitalization. An algorithm for selection of patients who warrant prophylactic implantation of an ICD is shown in Fig. 286-6.

Accelerated Idioventricular Rhythm Accelerated idioventricular rhythm (AIVR, “slow ventricular tachycardia”), a ventricular rhythm with a rate of 60–100 beats/min, often occurs transiently during fibrinolytic therapy at the time of reperfusion. For the most part, AIVR, whether it occurs in association with fibrinolytic therapy or spontaneously, is benign, and does not presage the development of classic ventricular tachycardia. Most episodes of AIVR do not require treatment if the patient is monitored carefully, as degeneration into a

more serious arrhythmia is rare; overly aggressive treatment can lead to complete heart block.

Supraventricular Arrhythmias Sinus tachycardia is the most common supraventricular arrhythmia. If it occurs secondary to another cause (such as anemia, fever, HF, or a metabolic derangement), the primary problem should be treated first. However, if it appears to be due to sympathetic overstimulation (e.g., as part of a hyperdynamic state), then treatment with a beta blocker is indicated. Other common arrhythmias in this group are atrial flutter and atrial fibrillation, which are often secondary to LV failure. Digoxin may be considered for supraventricular arrhythmias if HF with reduced ejection fraction is present. If left ventricular systolic dysfunction is absent, beta blockers, verapamil, and diltiazem are suitable alternatives for controlling the ventricular rate, as they may also help to control ischemia. If the abnormal rhythm persists for a prolonged period with a high ventricular rate (e.g., >120 beats/min) or if tachycardia induces HF, shock, or ischemia (as manifested by recurrent pain or ECG changes), a synchronized electroshock should be used.

Accelerated junctional rhythms have diverse causes but may occur in patients with inferoposterior infarction. Digitalis excess must be ruled out. In some patients with severely compromised LV function, the loss of appropriately timed atrial systole results in a marked reduction of cardiac output. Right atrial or coronary sinus pacing is indicated in such instances.

Sinus Bradycardia Treatment of sinus bradycardia is indicated if hemodynamic compromise results from the slow heart rate. Atropine is the most useful drug for increasing heart rate and should be given intravenously in doses of 1.0 mg initially. If the rate remains

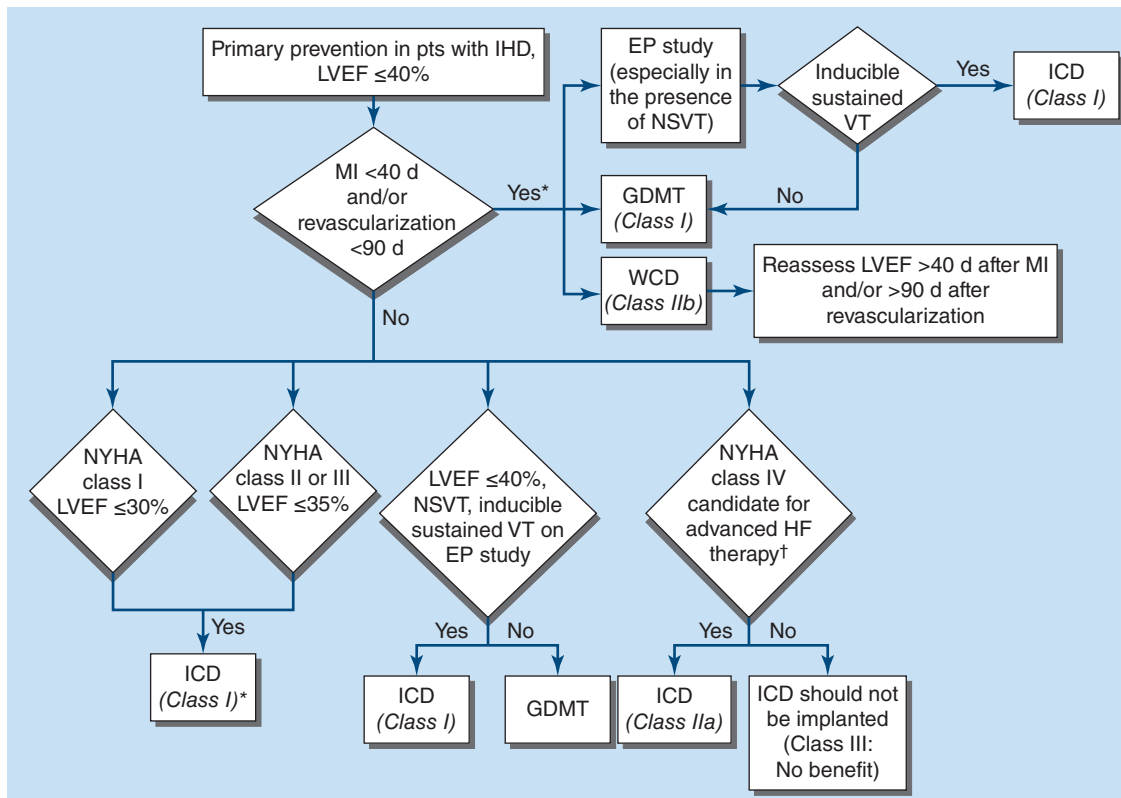


FIGURE 286-6 Primary prevention of SCD in patients with ischemic heart disease, including recent MI. *Scenarios exist for early ICD placement in select circumstances such as patients with a pacing indication or syncope. †Advanced HF therapy includes CRT, cardiac transplant, and left ventricular assist device. CRT, cardiac resynchronization therapy; EP, electrophysiologic; GDMT, guideline-directed management and therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; pts, patients; SCD, sudden cardiac death; VT, ventricular tachycardia; WCD, wearable cardioverter-defibrillator. The available evidence does not suggest there is a survival advantage to the use of an ICD early after MI, and the WCD is a potential option while waiting until the ejection fraction is reassessed (see figure). While the WCD appears to be effective in patients who wear the device, it is associated with frequent alarms, skin irritation, and emotional distress, which results in reduced wear time in a large number of patients. (Reproduced with permission from SM Al-Khatib et al: 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation* 138:e272, 2018.)

<50–60 beats/min, additional doses, up to a total of 3.0 mg, may be given. Persistent bradycardia (<40 beats/min) despite atropine may be treated with electrical pacing.

Atrioventricular and Intraventricular Conduction Disturbances (See also Chap. 251) Both the in-hospital mortality rate and the post-discharge mortality rate of patients who have complete atrioventricular (AV) block in association with anterior infarction are markedly higher than those of patients who develop AV block with inferior infarction. This difference is related to the fact that heart block in inferior infarction is commonly a result of increased vagal tone and/or the release of adenosine and, therefore, is transient. In anterior wall infarction, however, heart block is usually related to ischemic malfunction of the conduction system, which is commonly associated with extensive myocardial necrosis.

Temporary electrical pacing provides an effective means of increasing the heart rate of patients with bradycardia due to AV block. However, acceleration of the heart rate may have only a limited impact on prognosis in patients with anterior wall infarction and complete heart block in whom the large size of the infarct is the major factor determining outcome. It should be carried out if it improves hemodynamics. Pacing does appear to be beneficial in patients with inferoposterior infarction who have complete heart block associated with HF, hypotension, marked bradycardia, or significant ventricular ectopic activity. A subgroup of these patients, those with RV infarction, often respond poorly to ventricular pacing because of the loss of the atrial contribution to ventricular filling. In such patients, dual-chamber AV sequential pacing may be required.

External noninvasive pacing electrodes should be positioned in a “demand” mode for patients with sinus bradycardia (rate <50 beats/min) that is unresponsive to drug therapy, Mobitz II second-degree AV block, third-degree heart block, or bilateral bundle branch block (e.g., right bundle branch block plus left anterior fascicular block). Retrospective studies suggest that permanent pacing may reduce the long-term risk of sudden death due to bradyarrhythmias in the rare patient who develops combined persistent bifascicular and transient third-degree heart block during the acute phase of MI.

■ OTHER COMPLICATIONS

Recurrent Chest Discomfort Because recurrent or persistent ischemia often heralds extension of the original infarct or reinfarction in a new myocardial zone and is associated with a near tripling of mortality after STEMI, patients with these symptoms should be referred for prompt coronary arteriography and mechanical revascularization. Administration of a fibrinolytic agent is an alternative to early mechanical revascularization in patients with recurrent ischemic ST-segment elevation.

Pericarditis (See also Chap. 281) Pericardial friction rubs and/or pericardial pain are frequently encountered in patients with STEMI involving the epicardium. This complication can usually be managed with aspirin (650 mg four times daily). It is important to diagnose the chest pain of pericarditis accurately because failure to recognize it may lead to the erroneous diagnosis of recurrent ischemic pain and/or infarct extension, with resulting inappropriate use of anticoagulants, nitrates, beta blockers, or coronary arteriography. When it occurs, complaints of pain radiating to either trapezius muscle is helpful because such a pattern of discomfort is typical of pericarditis but rarely occurs with ischemic discomfort. Anticoagulants potentially could cause tamponade in the presence of acute pericarditis (as manifested by either pain or persistent rub) and therefore should not be used unless there is a compelling indication.

Thromboembolism Clinically apparent thromboembolism complicates STEMI in ~10% of cases, but embolic lesions are found in 20% of patients in necropsy series, suggesting that thromboembolism is often clinically silent. Thromboembolism is considered to be an important contributing cause of death in 25% of patients with STEMI who die after admission to the hospital. Arterial emboli originate from LV mural thrombi, while most pulmonary emboli arise in the leg veins.

Thromboembolism typically occurs in association with large infarcts (especially anterior), HF, and an LV thrombus detected by echocardiography. The incidence of arterial embolism from a clot originating in the ventricle at the site of an infarction is small but real. Two-dimensional echocardiography reveals LV thrombi in about one-third of patients with anterior wall infarction but in few patients with inferior or posterior infarction. Arterial embolism often presents as a major complication, such as hemiparesis when the cerebral circulation is involved. When a thrombus has been clearly demonstrated by echocardiographic or other techniques, systemic anticoagulation should be undertaken (in the absence of contraindications), as the incidence of embolic complications appears to be markedly lowered by such therapy. The appropriate duration of therapy is unknown, but 3–6 months is reasonable.

Left Ventricular Aneurysm The term *ventricular aneurysm* is usually used to describe *dyskinesis* or local expansile paradoxical wall motion. Normally functioning myocardial fibers must shorten more if stroke volume and cardiac output are to be maintained in patients with ventricular aneurysm; if they cannot, overall ventricular function is impaired. True aneurysms are composed of scar tissue and neither predispose to nor are associated with cardiac rupture.

The complications of LV aneurysm do not usually occur for weeks to months after STEMI; they include HF, arterial embolism, and ventricular arrhythmias. Apical aneurysms are the most common and the most easily detected by clinical examination. The physical finding of greatest value is a double, diffuse, or displaced apical impulse. Ventricular aneurysms are readily detected by two-dimensional echocardiography, which may also reveal a mural thrombus in an aneurysm.

Rarely, myocardial rupture may be contained by a local area of pericardium, along with organizing thrombus and hematoma. Over time, this *pseudoaneurysm* enlarges, maintaining communication with the LV cavity through a narrow neck. Because a pseudoaneurysm often ruptures spontaneously, it should be surgically repaired if recognized.

POSTINFARCTION RISK STRATIFICATION AND MANAGEMENT

Many clinical and laboratory factors have been identified that are associated with an increase in cardiovascular risk after initial recovery from STEMI. Some of the most important factors include persistent ischemia (spontaneous or provoked), depressed LV ejection fraction (<40%), rales above the lung bases on physical examination or congestion on chest imaging, and symptomatic ventricular arrhythmias. Other features associated with increased risk include a history of previous MI, age >75, diabetes mellitus, prolonged sinus tachycardia, hypotension, ST-segment changes at rest without angina (“silent ischemia”), an abnormal signal-averaged ECG, nonpatency of the infarct-related coronary artery (if angiography is undertaken), and persistent advanced heart block or a new intraventricular conduction abnormality on the ECG. Therapy must be individualized on the basis of the relative importance of the risk(s) present.

The goal of preventing reinfarction, pump failure, and death after recovery from STEMI has led to strategies to evaluate risk after infarction. The risk of early recurrent ischemic events has diminished substantially in the era of primary PCI, with further reduction in the setting of current practice recommendations for routine revascularization of suitable severely stenosed nonculprit coronary arteries. In contrast, in stable patients after fibrinolysis who have not undergone revascularization, submaximal exercise stress testing may be carried out before hospital discharge to detect residual ischemia and ventricular ectopy and to provide the patient with a guideline for exercise in the early recovery period. Alternatively, or in addition, a maximal (symptom-limited) exercise stress test may be carried out 4–6 weeks after infarction. Patients in whom angina is induced at relatively low workloads, those who have a large reversible defect on perfusion imaging, those with demonstrable ischemia, and those in whom exercise provokes symptomatic ventricular arrhythmias should be considered at high risk for recurrent MI or death from arrhythmia. Cardiac catheterization with coronary angiography and/or invasive electrophysiologic evaluation is advised.

Evaluation of LV function should be performed in all patients with STEMI. Recognition of a depressed LV ejection fraction by echocardiography, cardiac magnetic resonance imaging (MRI), or nuclear myocardial perfusion imaging (**Chap. 248**) identifies patients who should receive medications to inhibit the renin-angiotensin-aldosterone system. Cardiac MRI (**Chap. 248**) can provide high-resolution imaging of the extent of myocardial injury. A standard imaging agent (gadolinium) is administered, and images are obtained after a 10-min delay. Since little gadolinium enters the normal myocardium, where there are tightly packed myocytes, but does percolate into the intercellular region of the infarct zone, there is a bright signal in areas of infarction that appears in stark contrast to the dark areas of normal myocardium.

In many hospitals, a cardiac rehabilitation program with progressive exercise is initiated in the hospital and continued after discharge. Such programs should include an educational component that informs patients about their disease and its risk factors. Exercise testing performed at entry into cardiac rehabilitation also aids in formulating an individualized exercise prescription.

The usual duration of hospitalization for an uncomplicated STEMI is about 3–5 days. The remainder of the convalescent phase may be accomplished at home. During the first 1–2 weeks, the patient should be encouraged to increase activity by walking about the house and outdoors in good weather. Normal sexual activity may be resumed during this period. After 2 weeks, the physician should regulate the patient's activity on the basis of exercise tolerance. Most patients will be able to return to work within 2–4 weeks.

SECONDARY PREVENTION

Various secondary preventive measures are at least partly responsible for the improvement in the long-term mortality and morbidity rates after STEMI. Long-term treatment with an antiplatelet agent (usually aspirin) after STEMI is associated with a 25% reduction in the risk of recurrent infarction, stroke, or cardiovascular mortality (36 fewer events for every 1000 patients treated). Dual antiplatelet therapy with aspirin and a P2Y₁₂ receptor antagonist (clopidogrel, prasugrel, or ticagrelor) is recommended for 12 months after a STEMI, in the absence of high bleeding risk or the occurrence of bleeding complications. ACE inhibitors or ARBs and, in appropriate patients, aldosterone antagonists should be used indefinitely by patients with clinically evident HF, a reduced LV ejection fraction, or a large regional wall motion abnormality to prevent late ventricular remodeling and recurrent ischemic events.

After several decades of evaluation, there is substantial evidence that suggests that administration of an anticoagulant for secondary prevention has a favorable effect on late mortality, stroke, and reinfarction in patients hospitalized with STEMI. Nevertheless, given the multiple alternatives for antithrombotic therapy, including potent antiplatelet agents, for this indication, clinicians must weigh the potential benefits of treatment with an oral anticoagulant based on established indications for anticoagulation, the use of other antithrombotic therapies, including long-term dual antiplatelet therapy, and the risk for bleeding.

The chronic routine use of oral beta-adrenoceptor blockers for at least 1 year after STEMI is supported by well-conducted, placebo-controlled trials.

Anti-inflammatory therapy with low-dose colchicine (0.5 mg once daily) may be considered as part of a secondary preventive regimen for patients with STEMI, particularly if the patient has had a recurrent atherosclerotic vascular event despite guideline-directed medical therapy.

Finally, risk factors for *atherosclerosis* (**Chap. 244**) should be discussed with the patient and, when possible, favorably modified.

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287

Percutaneous Coronary Interventions and Other Interventional Procedures

Deepak L. Bhatt, Pinak B. Shah

Percutaneous transluminal coronary angioplasty (PTCA) was first introduced by Andreas Gruentzig in 1977 as an alternative to coronary bypass surgery. The concept was initially demonstrated by Charles Dotter in 1964 in peripheral vessels. The development of a small inelastic balloon catheter by Gruentzig allowed expansion of the technique into smaller peripheral and coronary vessels. Initial coronary experience was limited to single-vessel coronary disease and discrete proximal lesions due to the technical limitations of the equipment. Advances in technology with smaller profile balloon catheters and movable steerable guidewires and greater operator experience allowed the procedure to grow rapidly with expanded use in patients with more complex lesions and multivessel disease. The introduction of coronary stents in 1994 was one of the major advances in the field. These devices reduced acute complications and reduced by half the significant problems of acute thrombosis and late restenosis (or recurrence of stenosis). Further reductions in restenosis were achieved by the introduction of drug-eluting stents in 2003. These stents slowly release antiproliferative drugs directly into the plaque over a few months. Percutaneous coronary intervention (PCI) is the most common revascularization procedure in the United States and is performed more than twice as often as coronary artery bypass surgery: >900,000 patients a year.

Interventional cardiology is a separate discipline that began with coronary interventions. The discipline has now expanded to include interventions for structural heart disease including treatment of congenital heart disease and valvular heart disease; it also includes interventions to treat peripheral vascular disease, including atherosclerotic and nonatherosclerotic lesions in the carotid, renal, aortic, and peripheral arterial and venous circulations.

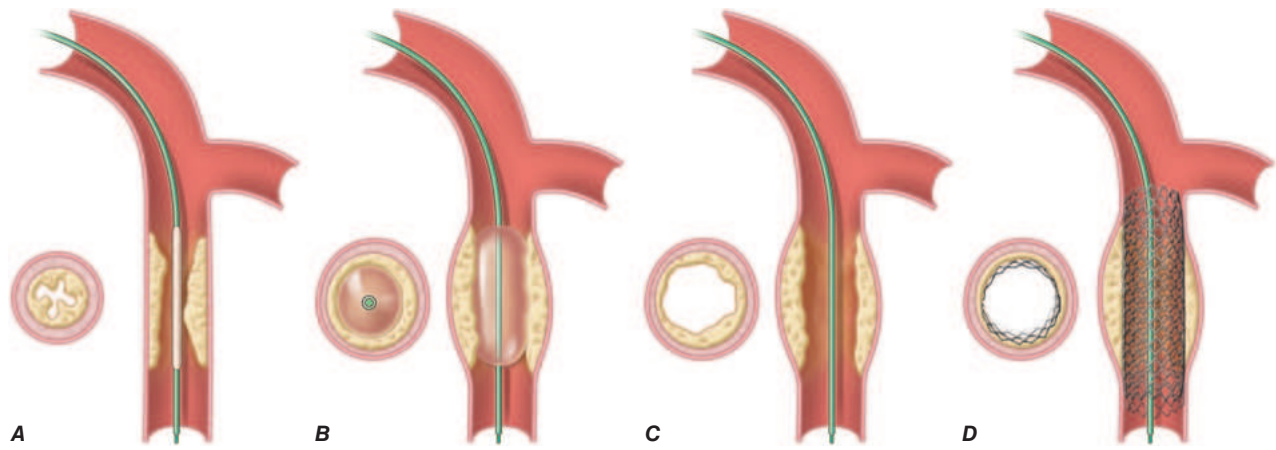


FIGURE 287-1 Schematic diagram of the primary mechanisms of balloon angioplasty and stenting. **A.** A balloon angioplasty catheter is positioned into the stenosis over a guidewire under fluoroscopic guidance. **B.** The balloon is inflated, temporarily occluding the vessel. **C.** The lumen is enlarged primarily by stretching the vessel, often resulting in small dissections in the neointima. **D.** A stent mounted on a deflated balloon is placed into the lesion and pressed against the vessel wall with balloon inflation (not shown). The balloon is deflated and removed, leaving the stent permanently against the wall acting as a scaffold to hold the dissections against the wall and prevent vessel recoil. (Reproduced with permission from EJ Topol: *Textbook of Cardiovascular Medicine*, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2002.)

TECHNIQUE

The initial procedure is performed in a similar manner as a diagnostic cardiac catheterization (**Chap. 249**). Arterial access is obtained via the radial or femoral artery. To prevent thrombotic complications during the procedure, patients who are anticipated to need PCI are given aspirin (325 mg) and may be given a platelet P2Y₁₂ inhibitor such as clopidogrel (loading dose of 600 mg), prasugrel (loading dose of 60 mg), or ticagrelor (loading dose of 180 mg) before the procedure. Cangrelor, a potent IV P2Y₁₂ inhibitor, is approved for use in patients who have not received an oral agent prior to the procedure. During the procedure, anticoagulation is achieved by administration of unfractionated heparin, enoxaparin (a low-molecular-weight heparin), or bivalirudin (a direct thrombin inhibitor). In patients with ST-segment elevation myocardial infarction (STEMI), high-risk acute coronary syndrome, or a large thrombus in the coronary artery, an intravenous glycoprotein IIb/IIIa inhibitor (tirofiban or eptifibatide) may also be given, although cangrelor appears to be as effective with less bleeding risk.

Following placement of an introducing sheath into the artery, preformed guiding catheters are used to cannulate selectively the origins of the coronary arteries. Through the guiding catheter, a flexible, steerable guidewire is negotiated into the coronary artery lumen using fluoroscopic guidance; it is then advanced through the stenosis and into the vessel

beyond. This guidewire then serves as a “rail” over which angioplasty balloons, stents, or other therapeutic devices can be advanced to enlarge the narrowed segment of coronary artery. The artery is usually dilated with a balloon catheter followed by placement of a stent. The catheters and introducing sheath are removed and the artery manually held, or in the case of radial access, an inflatable cuff is used. One of several femoral arterial closure devices can also be used to achieve hemostasis. Because PCI is usually performed under local anesthesia and mild sedation, procedural recovery is generally less than 24 h. Most patients undergoing elective PCI can be discharged the same day of the procedure.

Balloon angioplasty works by stretching the artery and displacing the plaque away from the lumen, enlarging the entire vessel (**Figs. 287-1 and 287-2**). The procedure rarely results in embolization of atherosclerotic material. Owing to inelastic elements in the plaque, the stretching of the vessel by the balloon results in small, localized dissections that can protrude into the lumen and be a nidus for acute thrombus formation. If the dissections are severe, then they can obstruct the lumen or induce a thrombotic occlusion of the artery (acute closure). Stents have largely prevented this complication by holding the dissection flaps up against the vessel wall (**Fig. 287-1**).

Stents are currently used in >90% of coronary angioplasty procedures. Stents are wire meshes (usually made of stainless steel or other

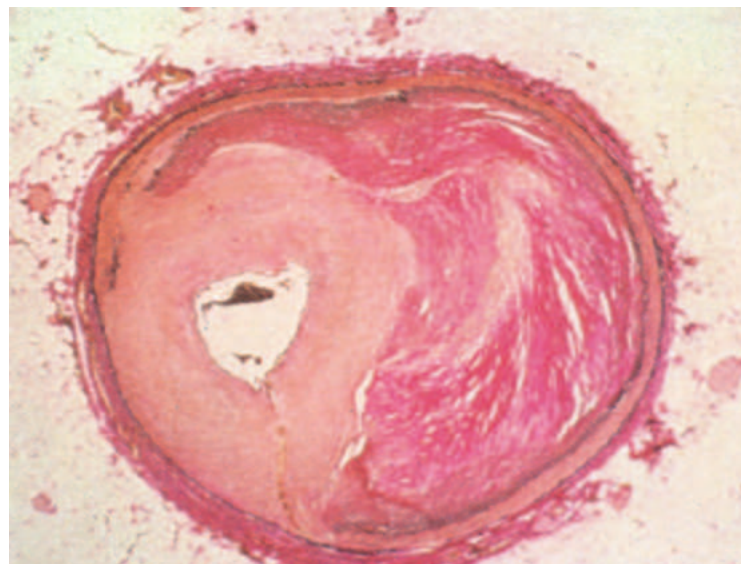


FIGURE 287-2 An example of neointimal hyperplasia and restenosis showing narrowing of the vessel. (Reprinted from CE Essed, M Van den Brand, AE Becker: *Transluminal coronary angioplasty and early restenosis. Fibrocellular occlusion after wall laceration. Br Heart J* 49:393, 1983; with permission.)

metals, such as cobalt chromium or nitinol) that are compressed over a deflated angioplasty balloon. When the balloon is inflated, the stent is enlarged to approximate the “normal” vessel lumen. The balloon is then deflated and removed, leaving the stent behind to provide a permanent scaffold in the artery. Owing to the design of the struts, these devices are flexible, allowing their passage through diseased and tortuous coronary vessels. Stents are rigid enough to prevent elastic recoil of the vessel and have dramatically improved the success and safety of the procedure as a result.

Drug-eluting stents (DESs) further enhanced the efficacy of PCI. An antiproliferative agent is attached to the metal stent by use of a thin polymer coating. The antiproliferative drug elutes from the stent over a 1- to 3-month period or longer after implantation. DESs have been shown to reduce clinical restenosis by 50%, so that in uncomplicated lesions, symptomatic restenosis occurs in 5–10% of patients. Not surprisingly, this benefit led to the rapid acceptance of these devices, and given their safety profile, nearly 100% of stents placed today are DESs. The first-generation DESs were coated with either sirolimus or paclitaxel. Second-generation DESs use newer agents such as everolimus, biolimus, and zotarolimus. These second-generation DESs appear to be more effective with fewer complications, such as early or late stent thrombosis, than the first-generation devices and, therefore, have replaced the first-generation stents. Biodegradable polymers that are used to attach the drugs to the stents may be theoretically superior to permanent polymers in preventing late stent thrombosis. In addition, the first-generation everolimus-eluting biodegradable vascular scaffold (BVS) stent had been shown to be reasonably safe with gradual degradation over several years, although concerns about late and very late stent thrombosis ultimately prevented introduction into clinical practice in the United States. Additional bioresorbable stents are under investigation. Drug-coated balloons (DCBs) are covered with an antiproliferative drug that can also reduce restenosis and are used primarily to treat in-stent restenosis.

Other interventional devices include atherectomy devices, thrombectomy catheters, and intravascular lithotripsy (IVL). These devices are designed to modify complex plaque or thrombus to facilitate and optimize stent placement. Rotational atherectomy is the most commonly used adjunctive device and is modeled after a dentist's drill, with small round burs of 1.25–2.5 mm at the tip of a flexible wire shaft. The burr is passed over the guidewire up to the stenosis and drills atherosclerotic material. Because the atherosclerotic particles are $\leq 25 \mu\text{m}$, they pass through the coronary microcirculation and rarely result in complications. The device is particularly useful in heavily calcified plaques that are resistant to balloon dilatation. Orbital atherectomy is a newer approach to calcified lesions that also relies on a spinning burr. IVL catheters emit pressure waves that fracture calcium within vessel walls, thereby increasing the compliance of the vessel and enhancing stent deployment. In acute STEMI, specialized catheters without a balloon can be used to aspirate thrombus in order to prevent embolization down the coronary vessel and to improve blood flow before angioplasty and stent placement. Current studies show that manual catheter thrombus aspiration should not be used routinely but, in certain cases of a large thrombus burden, can improve blood flow in primary PCI.

PCI of degenerated saphenous vein graft lesions has been associated with a significant incidence of distal embolization of atherosclerotic material, unlike PCI of native vessel disease. A number of distal protection devices have been shown to significantly reduce embolization and myocardial infarction in this setting. Most devices work by using a collapsible wire filter at the end of a guidewire that is expanded in the distal vessel before PCI. If atherosclerotic debris is dislodged, the basket captures the material, and at the end of the PCI, the basket is pulled into a delivery catheter, and the debris safely removed from the patient.

Intravascular imaging is an adjunct to angiographic imaging for PCI that provides information regarding optimal treatment strategy and improves the long-term durability and safety of PCI. There are two modalities available for intravascular imaging: intravascular ultrasound (IVUS) and optical coherence tomography (OCT). IVUS catheters have piezoelectric ultrasound transducers at the distal end that can provide an image from within the vessel, as well as provide

information regarding plaque morphology. OCT utilizes near-infrared light to provide intraluminal imaging of the vessel. The resolution of OCT is better than IVUS; however, both modalities have been shown in meta-analyses of clinical trials to optimize stent diameters and reduce the likelihood of delayed complications, such as in-stent restenosis and stent thrombosis.

SUCCESS AND COMPLICATIONS

A successful procedure (angiographic success), defined as a reduction of the stenosis to less than a 20% diameter narrowing, occurs in 95–99% of patients. Lower success rates are seen in patients with tortuous, small, or calcified vessels or chronic total occlusions. Chronic total occlusions have the lowest success rates, and their recanalization is significantly better if the occlusion is recent (within 3 months) or there are favorable anatomic features. Improvements in equipment and complex antegrade and retrograde wire crossing techniques have increased the success rates of recanalization of chronic total occlusions to 70–80%.

Serious complications are rare but include a mortality rate of 0.1–0.3% for elective cases, a large myocardial infarction in <3%, and stroke in 0.1–0.4%. Patients who are older (>65 years), undergoing an emergent or urgent procedure, have chronic kidney disease, present with STEMI, or are in shock have significantly higher risk. Scoring systems can help to estimate the risk of the procedure. Myocardial infarction during PCI can occur for multiple reasons including an acute occluding thrombus, severe coronary dissection, embolization of thrombus or atherosclerotic material with resulting (micro) vascular occlusion, or closure of a side branch vessel at the site of angioplasty or stent placement. Most myocardial infarctions are small and only detected by a rise in the creatine phosphokinase (CPK) or troponin level after the procedure. Only those with significant enzyme elevations (>10 times the upper limit of normal) are associated with a less favorable long-term outcome. Coronary stents have largely prevented occlusive coronary dissections from angioplasty due to the scaffolding effect of the stent.

All types of stents are prone to stent thrombosis (1–3%), either acute (<24 h) or subacute (1–30 days), which can be ameliorated by greater attention to full initial stent deployment and the use of dual antiplatelet therapy (DAPT) (aspirin plus a platelet P2Y₁₂ receptor blocker [clopidogrel, prasugrel, or ticagrelor]). Late (30 days–1 year) and very late (>1 year) stent thromboses occur very infrequently with stents but are slightly more common with first-generation DESs. Use of the second-generation stents is associated with lower rates of late and very late stent thromboses, and shorter durations of DAPT (6 months) are recommended for the stent, although longer durations may be useful depending on the underlying atherothrombotic and bleeding risks. Longer durations of DAPT up to 1 year should also be considered for patients undergoing PCI for acute coronary syndromes. Premature discontinuation of DAPT, particularly in the first month after implantation, is associated with a significantly increased risk for stent thrombosis (three- to nine-fold greater). Stent thrombosis results in death in 10–20% and myocardial infarction in 30–70% of patients. Elective surgery that requires discontinuation of antiplatelet therapy after DES implantation should be postponed until after 3 months and preferably after 6 months, if at all possible.

Restenosis, or renarrowing of the dilated coronary stenosis, is the most common complication of PCI and occurs in 20–50% of patients with balloon angioplasty alone, 10–30% of patients with bare metal stents, and 5–15% of patients with DESs within the first year. The fact that stent placement provides a larger acute luminal area than balloon angioplasty alone reduces the incidence of subsequent restenosis. DESs further reduce restenosis through a reduction in excessive neointimal growth over the stent. If restenosis does not occur, the long-term outcome is excellent (Fig. 287-3). Clinical restenosis is recognized by recurrence of angina or symptoms within 12 months of the procedure. Less frequently, patients with restenosis can present with non-ST-segment elevation myocardial infarction (NSTEMI) (10%) or STEMI (2%) as well. Very late stent thrombosis and restenosis after 1 year are more likely to be due to neoatherosclerosis than intimal hyperplasia seen within the first year. Clinical restenosis requires confirmation of a significant stenosis at the site of the prior PCI. The

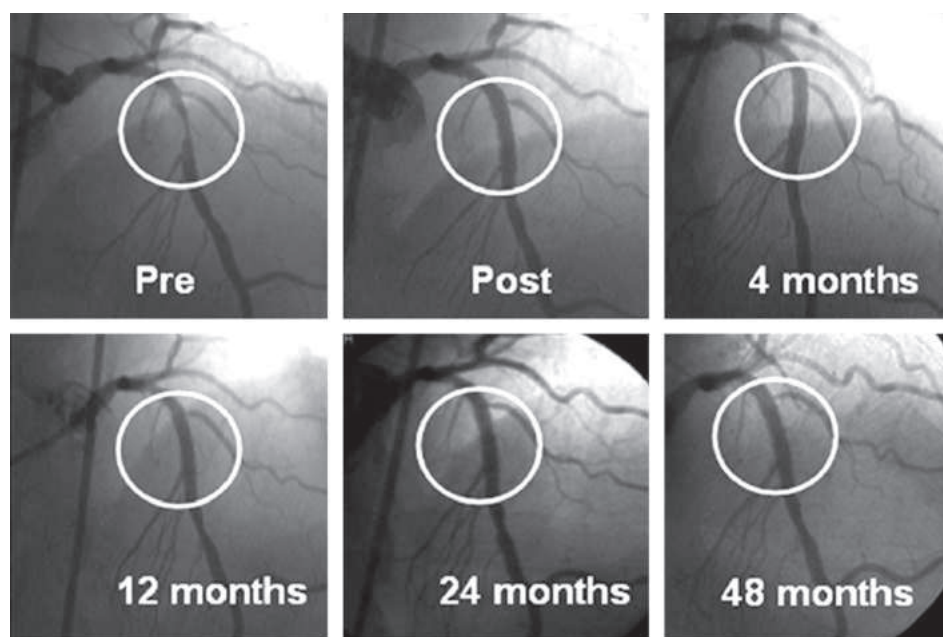


FIGURE 287-3 Long-term results from one of the first patients to receive a sirolimus-eluting stent from early Sao Paulo experience. (From GW Stone, in D Baim [ed]: *Cardiac Catheterization, Angiography and Intervention*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2006; with permission.)

management of clinical restenosis is usually to repeat the PCI with balloon dilatation and placement of another DES. Once a patient has had restenosis, the risk of a second restenosis is further increased. The risk factors for restenosis are diabetes, myocardial infarction, long lesions, small-diameter vessels, and suboptimal initial PCI result. Treatments for symptomatic recurrent restenosis include re-stenting, brachytherapy, DCBs, or coronary bypass surgery.

INDICATIONS

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines extensively review the indications for PCI in patients with stable angina, unstable angina, NSTEMI, and STEMI and should be referred to for a comprehensive discussion of the indications. Briefly, the two principal indications for coronary revascularization in patients with *chronic stable angina* (Chap. 284) are (1) to improve angina symptoms in patients who remain symptomatic despite adequate medical therapy and (2) to reduce mortality rates in patients with severe and extensive coronary disease. In patients with stable angina who are well controlled on medical therapy, studies such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trials have shown that initial revascularization does not lead to better outcomes (death or myocardial infarction) and can be safely delayed until symptoms worsen or evidence of severe ischemia on noninvasive testing occurs. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial was the largest trial comparing optimal medical therapy to revascularization with PCI or coronary artery bypass grafting (CABG) in stable patients with moderate ischemia on stress testing but without left main disease or reduced left ventricular function (<35% ejection fraction). It showed that optimal medical therapy was similar to revascularization in a composite of cardiovascular death or hospitalization or in cardiovascular death and myocardial infarction at a median of 3.3 years. This trial confirms prior studies and supports conservative management in most stable patients. When revascularization is indicated due to unacceptable symptoms, the choice of PCI or CABG depends on a number of clinical and anatomic factors.

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial compared PCI with the paclitaxel DES to CABG in 1800 patients with three-vessel coronary disease or left main disease. The study found no difference in death or myocardial infarction at 1 year, but repeat revascularization was

significantly higher in the stent-treated group (13.5 vs 5.9%), while stroke was significantly higher in the surgical group (2.2 vs 0.6%). The primary endpoint of death, myocardial infarction, stroke, or revascularization was significantly better with CABG, particularly in those with the most extensive coronary artery disease such as three-vessel disease. The 10-year results confirm these findings. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 patients with diabetes and multivessel disease and found a significantly lower primary endpoint of death, myocardial infarction, or stroke with CABG than PCI. Recent trials comparing PCI with CABG have shown similar outcomes for those with less extensive disease, but a better outcome with CABG when the coronary disease is severe and extensive. These studies support CABG for those with the most severe left main and three-vessel disease or those with diabetes. Lesser degrees of multivessel disease in patients with or without diabetes have an equal outcome with PCI, including left main disease with favorable angiographic characteristics.

The choice of PCI versus CABG is also related to the anticipated procedural success and complications of PCI and the risks of CABG. For PCI, the characteristics of the coronary anatomy are critically important. The location of the lesion in the vessel (proximal or distal), the degree of tortuosity, and the size of the vessel are considered. In addition, the lesion characteristics, including the degree of the stenosis, the presence of calcium, lesion length, and presence of thrombus, are assessed. The most common reason to decide not to do PCI is that the lesion(s) felt to be responsible for the patient's symptoms is not treatable. This is most commonly due to the presence of a chronic total occlusion (>3 months in duration) with unfavorable characteristics. A lesion classification to characterize the likelihood of success or failure of PCI has been developed by the ACC/AHA. Lesions with the highest success are called type A lesions (such as proximal noncalcified subtotal lesions), and those with the lowest success or highest complication rate are type C lesions (such as chronic total occlusions). Intermediate lesions are classified as type B1 or B2 depending on the number of unfavorable characteristics. Approximately 25–30% of patients will not be candidates for PCI due to unfavorable anatomy, whereas only 5% of CABG patients will not be candidates for surgery due to coronary anatomy. The primary reason for being considered inoperable with CABG is the presence of severe comorbidities such as advanced age, frailty, severe chronic obstructive pulmonary disease (COPD), poor left ventricular function or lack of suitable surgical conduits, or poor distal targets for bypass.

Another consideration in choosing a revascularization strategy is the degree of revascularization needed. In patients with multivessel disease, bypass grafts can usually be placed to all vessels >2 mm with significant stenosis, whereas PCI may be able to treat only some of the lesions due to the presence of unfavorable anatomy. Assessment of the significance of intermediate lesions using fractional flow reserve (FFR) or the instantaneous wave-free ratio (iFR) ([Chap. 249](#)) can assist in determining which lesions should be revascularized. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial showed a 30% reduction in adverse events when revascularization by PCI was restricted to those lesions that were hemodynamically significant ($\text{FFR} \leq 0.80$) rather than when guided by angiography alone. Trials have shown that iFR is as predictive as FFR but is quicker and easier to perform, especially if there are sequential lesions or multivessel disease. Thus, complete revascularization of all functionally significant lesions should be favored and considered when choosing the optimal revascularization strategy. Given the multiple factors that need to be considered in choosing the best revascularization for an individual patient with multivessel disease, it is optimal to have a discussion among the cardiac surgeon, interventional cardiologist, and the physicians caring for the patient (so-called heart team) to weigh the choices properly.

Patients with acute coronary syndrome are at excess risk of short- and long-term mortality. Randomized clinical trials have shown that PCI is superior to intensive medical therapy in reducing mortality and myocardial infarction, with the benefit largely confined to those patients who are high risk. High-risk non-ST-segment elevation acute coronary syndrome patients are defined as those with any one of the following: refractory ischemia, recurrent angina, positive cardiac-specific enzymes, new ST-segment depression, transient ST-segment elevation, low ejection fraction, severe arrhythmias, or a recent PCI or CABG. PCI is preferred over surgical therapy in most high-risk patients with acute coronary syndromes unless they have severe multivessel disease or the culprit lesion responsible for the unstable presentation cannot be adequately determined or treated. In STEMI, thrombolysis and PCI (primary PCI) are effective methods to restore coronary blood flow and salvage myocardium within the first 12 h after onset of chest pain. Because PCI is more effective in restoring flow than thrombolysis, it is preferred if readily available within 90 min of presentation to the hospital. PCI is also performed following thrombolysis to facilitate adequate reperfusion or as a rescue procedure in those who do not achieve reperfusion from thrombolysis, who cannot be rapidly transferred to a hospital that can perform primary PCI, or who develop cardiogenic shock. The Complete Versus Culprit-Only

Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI (COMPLETE) trial supports complete revascularization of nonculprit lesions in STEMI either in the hospital or in the few weeks after discharge.

OTHER INTERVENTIONAL TECHNIQUES

■ STRUCTURAL HEART DISEASE

Interventional treatment for structural heart disease (adult congenital heart disease and valvular heart disease) is a significant and growing component of the field of interventional cardiology.

The most common adult congenital lesion to be treated with percutaneous techniques is closure of atrial septal defects ([Chap. 280](#)). The procedure is done as in a diagnostic right heart catheterization with the passage of a catheter up the femoral vein into the right atrium. With echo and fluoroscopic guidance, the size and location of the defect can be accurately defined, and closure is accomplished using one of several approved devices. All devices use a left atrial and right atrial wire mesh or covered disk that are pulled together to capture the atrial septum around the defect and seal it off. The Amplatzer Septal Occluder (AGA Medical, Minneapolis, MN) and the Gore ASD Occluder (W.L. Gore, Flagstaff, AZ) are the most commonly used devices in the United States ([Fig. 287-4](#)). The success rate in selected patients is 85–95%, and the device complications are rare and include device embolization, infection, or erosion. Closure of patent foramen ovale (PFO) is done in a similar fashion. PFO closure may be considered in patients who have had recurrent paradoxical stroke or transient ischemic attack (TIA) despite adequate medical therapy including anticoagulation or antiplatelet therapy or who are at high risk for recurrent stroke. Ten-year follow-up from the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial showed a benefit of closure in reducing the risk for recurrent cryptogenic stroke, as have the REDUCE and CLOSE trials. The use in the treatment of migraine is not supported by the current data.

Similar devices can also be used to close patent ductus arteriosus and ventricular septal defects. Other congenital diseases that can be treated percutaneously include coarctation of the aorta, pulmonic stenosis, peripheral pulmonary stenosis, and other abnormal communications between the cardiac chambers or vessels.

The treatment of valvular heart disease is the most rapidly growing area in interventional cardiology. In the past, the only available techniques were balloon valvuloplasty for the treatment of aortic, mitral, or pulmonic stenosis ([Chap. 272](#)). Mitral valvuloplasty is the preferred treatment for symptomatic patients with rheumatic mitral stenosis

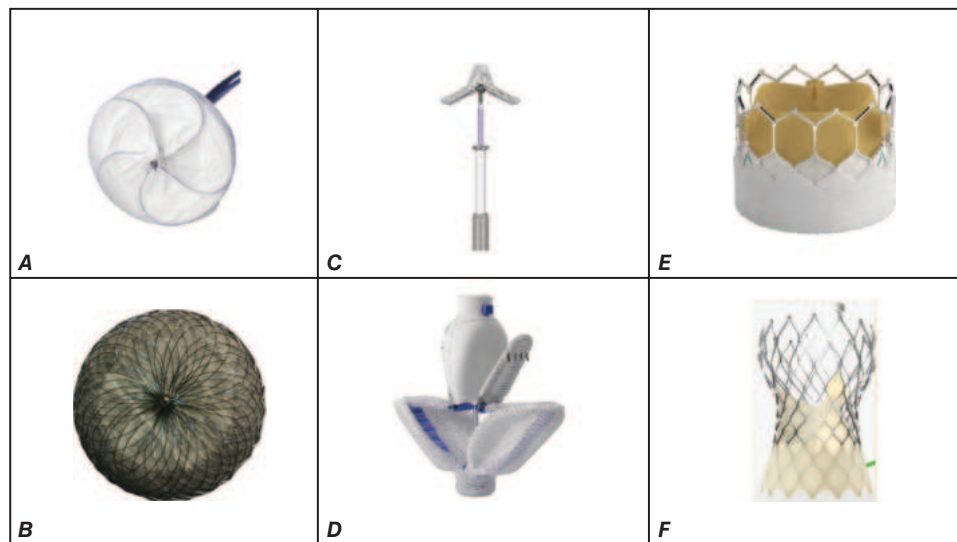


FIGURE 287-4 Devices commonly used for structural heart procedures. **A.** Gore Atrial Septal Occluder. (Reproduced with permission from W.L. Gore.) **B.** Amplatzer ASD Occluder. (Reproduced with permission from Abbott.) **C.** MitraClip. (Reproduced with permission from Abbott.) **D.** Pascal. (Reproduced with permission from Edwards Lifesciences.) **E.** Sapien 3 Ultra. (Reproduced with permission from Edwards Lifesciences.) **F.** Evolut FX. (Reproduced with permission from Medtronic.)

who have favorable anatomy. The outcome in these patients is equal to that of surgical commissurotomy. The success is highly related to the echocardiographic appearance of the valve. The most favorable setting is commissural fusion without calcification or subchordal fusion and the absence of significant mitral regurgitation. Access is obtained from the femoral vein using a transseptal technique in which a long metal catheter with a needle tip is advanced from the femoral vein through the right atrium and atrial septum at the level of the foramen ovale into the left atrium. A balloon-dilatation catheter is negotiated across the mitral valve and inflated to a predetermined size to enlarge the valve. The most commonly used dilatation catheter is the Inoue balloon. The technique splits the commissural fusion and commonly results in a doubling of the mitral valve area. The success of the procedure in favorable anatomy is 95%, and severe complications are rare (1–2%). The most common complications are tamponade due to puncture into the pericardium during the transseptal puncture or the creation of severe mitral regurgitation due to damage to the valve leaflets.

Severe mitral regurgitation can be treated percutaneously using transcatheter edge-to-edge repair (TEER). There are two devices approved for TEER including the MitraClip (Abbott, Abbott Park, IL) and the PASCAL device (Edwards Lifescience, Irvine, CA) (Fig. 287-4). The procedure involves the passage of a catheter into the left atrium using the transseptal technique. A special catheter with a metallic clamping device on the end is passed through the mitral valve and retracted to catch and bring together the mid portion of the anterior and posterior mitral valve leaflets. The device creates a double opening in the mitral valve and thereby reduces mitral regurgitation similar to the surgical Alfieri repair. In the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) trial, the MitraClip device was less effective than surgical repair or replacement but was shown to be safe. Subsequent trials have shown it to be reasonably effective for patients who are not good candidates for surgical repair, particularly when the regurgitation is due to functional causes. The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial showed that, in patients with heart failure and functional mitral regurgitation who were carefully selected based on clinical and echocardiographic features, the procedure can reduce mortality.

At the present time, there are no approved devices for transcatheter mitral valve replacement (TMVR of native mitral valves). There are many devices presently in clinical trials. TMVR device development has been challenging due to the interior location of the mitral valve, the large size of the mitral valve, and potential for left ventricular outflow tract obstruction.

Severe aortic stenosis can be treated with balloon valvuloplasty as well. In this setting, the valvuloplasty balloon catheter is placed retrograde across the aortic valve from the femoral artery and briefly inflated to stretch open the valve. The success is much less favorable, with only 50% achieving an aortic valve area of $>1 \text{ cm}^2$ and a restenosis rate of 25–50% after 6–12 months. This poor success rate has limited its use to patients who are not surgical candidates or as a bridge to surgery or transcatheter aortic valve replacement (TAVR). In this setting, the intermediate-term mortality rate of the procedure is high (10%). Repeat aortic valvuloplasty as a treatment for aortic valve restenosis has been reported.

TAVR has been shown to be an effective treatment for low-, intermediate-, and high-risk patients and inoperable patients with aortic stenosis. Currently, three valve devices are approved in the United States: the Edwards SAPIEN valve (Edwards Lifescience, Irvine, CA), the Evolut platform (Medtronic, Minneapolis, MN), and the Navitor system (Abbott Cardiovascular, Plymouth, MN) (Fig. 287-4). Data to date show excellent durability of the valves, although long-term outcomes of 10 years are not yet available. The Evolut and Navitor valves are self-expanding, whereas the Sapien valve is balloon

expanded. The cannulas are large (14–18 French), and retrograde access via the femoral artery is most commonly utilized. In patients with peripheral artery disease, access via the axillary or carotid artery may be utilized. The valve is positioned across the valve and deployed, occasionally requiring postdeployment balloon inflation to ensure full contact with the aortic annulus. The success rate is $>90\%$, and the 30-day mortality rate is 2–15% based on preoperative risk. The Placement of Aortic Transcatheter Valve (PARTNER) randomized trial of the Edwards valve showed a 55% reduction in 1-year mortality and major adverse events in the extreme-risk group randomized to TAVR compared with medical therapy. In separate randomized trials comparing the Sapien platform to surgery and the Evolut platform to surgery, low-, moderate-, and high-risk patients had similar outcomes to surgical valve replacement at 1 year. As a result, these valves have been approved for low-, intermediate-, high-, and extreme-risk patients with severe symptomatic aortic stenosis. At the present time, the Navitor platform is only approved for patients at high risk for surgery.

Aortic and mitral bioprosthetic valve degeneration can be treated with repeat surgery or, in high-risk patients, with a transcatheter valve-in-valve procedure where a percutaneous valve is placed inside of the prior surgical valve. It has been shown to be effective for aortic and mitral valves.

Pulmonic stenosis can also be effectively treated with balloon valvuloplasty and percutaneously replaced with the Melody valve (Medtronic). Tricuspid valve interventions are increasingly being performed utilizing TEER and tricuspid valve replacement devices, which are now approved for use.

PERIPHERAL ARTERY INTERVENTIONS

The use of percutaneous interventions to treat symptomatic patients with arterial obstruction in the carotid, renal, aortic, and peripheral vessels is an effective alternative to vascular surgery. Randomized clinical trial data support the use of carotid stenting in patients at high risk of complications from carotid endarterectomy (Fig. 287-5). Recent trials suggest similar outcomes with carotid stenting and carotid endarterectomy in patients at average risk, although depending on the patient's risk for periprocedural stroke or myocardial infarction, one procedure may be preferred over the other. The success rate of peripheral artery interventional procedures has been improving, including treatment for long segments of occlusive disease historically treated by peripheral bypass surgery (Fig. 287-6). The use of DCBs and DESs has been shown to reduce restenosis when compared with balloon angioplasty alone. Peripheral intervention is increasingly part of the training of an interventional cardiologist, and most programs now require an additional year of training after the interventional cardiology training year. The techniques and outcomes are described in detail in the chapter on peripheral vascular disease (Chap. 292).

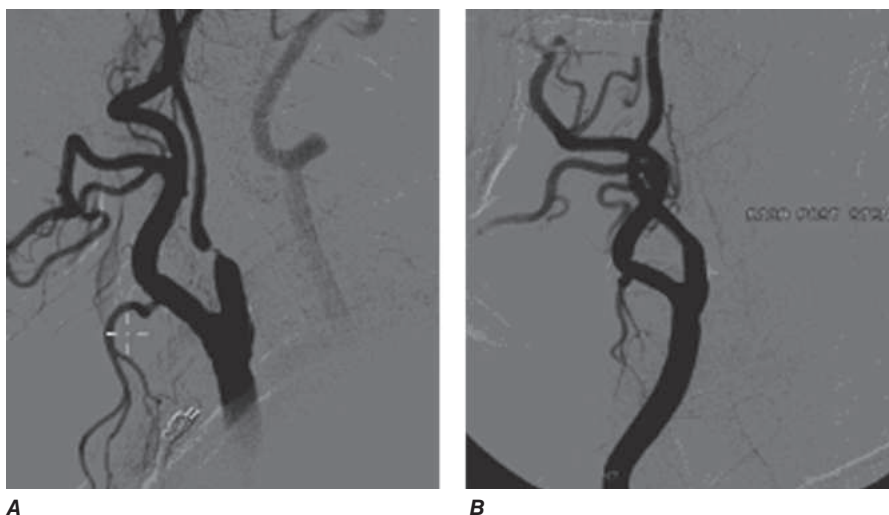


FIGURE 287-5 **A.** An example of a high-risk patient who requires carotid revascularization but who is not a candidate for carotid endarterectomy. **B.** Carotid artery stenting resulted in an excellent angiographic result. (From M Belkin, DL Bhatt: Carotid stenting in the elderly: Is 80 the new 60? *Circulation* 119:2302; 2009; with permission.)

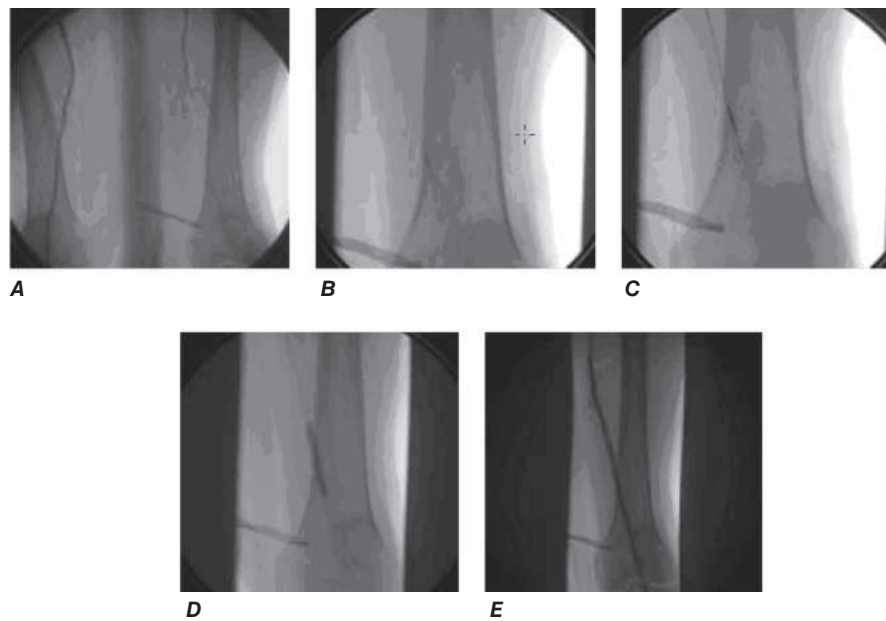


FIGURE 287-6 Peripheral interventional procedures have become highly effective at treating anatomic lesions previously amenable only to bypass surgery. **A.** Complete occlusion of the left superficial femoral artery. **B.** Wire and catheter advanced into subintimal space. **C.** Intravascular ultrasound positioned in the subintimal space to guide retrograde wire placement through the occluded vessel. **D.** Balloon dilation of the occlusion. **E.** Stent placement with excellent angiographic result. (Reprinted from A Almahameed, DL Bhatt: Contemporary management of peripheral arterial disease: III. Endovascular and surgical management. *Cleve Clin J Med* 2006;73(suppl 4):S45-S51. With permission from The Cleveland Clinic Foundation. © 2006. The Cleveland Clinic Foundation. All rights reserved.)

■ CIRCULATORY SUPPORT TECHNIQUES

The use of circulatory support techniques is indicated for the management of patients with shock or hemodynamic instability and occasionally is needed in order to safely perform PCI on hemodynamically unstable patients. It also can be useful in helping to stabilize patients before surgical interventions. The most commonly used device is the percutaneous intraaortic balloon pump developed in the early 1960s. A 7- to 8-French, 25- to 50-mL balloon catheter is placed retrograde from the femoral artery into the descending aorta between the aortic arch and the abdominal aortic bifurcation. It is connected to a helium gas inflation system that synchronizes the inflation to coincide with early diastole with deflation by mid-diastole. As a result, it increases early diastolic pressure, lowers systolic pressure, and lowers late diastolic pressure through displacement of blood from the descending aorta (counterpulsation). This results in an increase in coronary blood flow and a decrease in afterload. It is contraindicated in patients with aortic regurgitation, aortic dissection, or severe peripheral artery disease. The major complications are vascular and thrombotic. Intravenous heparin is given in order to reduce thrombotic complications.

Another support device is the Impella (Abiomed, Danvers, MA). The Impella CP catheter is placed percutaneously from the femoral artery into the left ventricle. The catheter has a small microaxial pump at its tip that can pump up to 2.5–5 L/min from the left ventricle to the aorta. The larger Impella 5.5 device provides greater support for longer periods of time but requires surgical implantation typically through the axillary artery. Patients can also be placed on peripheral extracorporeal membrane oxygenation (ECMO) using large cannulas placed in the femoral artery and vein. This technique can be performed emergently or electively in the catheterization laboratory and is useful for support of patients with acute respiratory failure or cardiac failure.

■ INTERVENTIONS FOR PULMONARY EMBOLISM

The treatment of deep vein thrombosis is intravenous anticoagulation, with placement of an inferior vena cava filter if recurrent pulmonary emboli (PE) occur or anticoagulation is not possible. Postphlebotic syndrome is a serious condition due to chronic venous obstruction that can lead to chronic leg edema and venous ulcers. Randomized data show that mechanical treatments may have a selective role in treatment of large iliofemoral deep-vein thrombosis.

PE should be treated with fibrinolytic agents if massive and in some cases if submassive. Surgical pulmonary embolectomy is an option for the treatment of massive PE with hemodynamic instability in patients who have contraindications for systemic fibrinolysis or those in whom it has failed. Catheter-based therapies for submassive and massive PEs are still evolving, but studies have shown promise. The techniques employed include catheter directed thrombolysis with intraclot infusion of a thrombolytic agent, potentially enhanced with ultrasound-assisted catheter-directed thrombus fragmentation. The success of these techniques has been reported to be 80–90%, with major complications occurring in 2–4% of patients. Thrombus removal with large-bore aspiration devices include the FlowTrieve (Inari Medical, Irvine, CA) and the CAT12 (Penumbra, Alameda, CA).

■ INTERVENTIONS FOR REFRACTORY HYPERTENSION

The recent recognition of the importance of the renal sympathetic nerves in modulating blood pressure has led to a technique to selectively denervate renal sympathetic nerves in patients with refractory hypertension. The procedure involves applying low-power radiofrequency treatment via a catheter along the length of both renal arteries. Despite promising nonrandomized data, in the randomized Symplicity HTN-3 trial, renal denervation did not significantly reduce blood pressure compared with medical therapy. Further optimization of the technique is ongoing with some evidence from small, randomized trials of modest efficacy, which was sufficient to lead to regulatory approval.

CONCLUSION

Interventional cardiology continues to expand its borders. Treatment for coronary artery disease, including complex anatomic subsets, continues to advance. Technological advances such as DESs, now already in their second generation, are improving the results of PCI. PCI is the treatment of choice for patients with acute coronary syndromes. For patients with stable coronary disease, PCI is effective in symptom alleviation. Use of a Heart Team is the best way to make decisions concerning which revascularization—PCI or CABG—is best for an individual patient. Treatment of peripheral and cerebrovascular disease can be effective with percutaneous techniques. Structural heart disease is increasingly being treated with percutaneous options, with interventional approaches such as TAVR becoming preferred over surgical aortic valve replacement. Further growth of invasive procedures is anticipated in years to come.

FURTHER READING

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288 Hypertension

Paul K. Whelton

High blood pressure (BP) is a leading risk factor for cardiovascular disease (CVD), including ischemic and hemorrhagic stroke, coronary heart disease (CHD), heart failure (HF), peripheral arterial disease (PAD), chronic kidney disease (CKD)/end-stage kidney disease (ESKD), dementia, and all-cause mortality. Hypertension, a subset of high BP, is very common no matter how it is defined and results in a huge burden due to death, morbidity, disability, social and workplace disruption, and cost to the individual and society. According to data from the National Ambulatory Medical Care Survey (NAMCS), hypertension is a component for more than one-third of all visits to office-based physicians by U.S. adults. Likewise, global estimates have ranked hypertension as the most common reason for primary care visits worldwide. Hypertension is often associated with other CVD risk factors, resulting in a higher risk of complications and related burden of illness. The optimal approach to high BP is to prevent its development, but diagnosis, treatment, and control of hypertension also provide an effective means to reduce the risk of BP-related CVD. Unfortunately, both strategies are poorly implemented worldwide, resulting in a high burden of preventable disease.

BLOOD PRESSURE PHYSIOLOGY AND PATHOPHYSIOLOGY

Complex and incompletely understood mechanisms control blood flow in individual organs and the arteriolar system. At the most basic level, arterial BP is controlled by cardiac output and peripheral resistance (Fig. 288-1). However, arterial pressure is largely thought to be controlled by a renal-volume-endocrine pressure control system, in which the blood volume and total peripheral resistance are manipulated slowly to adjust arterial BP.

Cardiac output is influenced by stroke volume and heart rate, with stroke volume being related to myocardial contraction and the size of the intravascular compartment. Changes in cardiac output play an important role in acute BP responses to stressors. Peripheral vascular resistance is determined by functional and anatomic changes in small arteries and arterioles. The vascular endothelium is composed of a single layer of endothelial cells that constitute the inner cellular lining of arterioles. It serves as a direct contact with circulating blood and regulates exchanges between the bloodstream and surrounding tissues. Endothelial cells control vascular tone and, thereby, blood flow by synthesizing and releasing relaxing and contracting factors such as nitric oxide; metabolites of arachidonic, lipoxygenase, and cytochrome pathways; peptides, including endothelin; adenosine; purines; and reactive oxygen species; and by generating endothelial enzymes that produce vasoactive hormones such as angiotensin II. Endothelial dysfunction may play an important role in the initiation or progression of hypertension and atherosclerosis. A wide variety of systems interplay to keep cardiac output and peripheral resistance in balance, including sodium

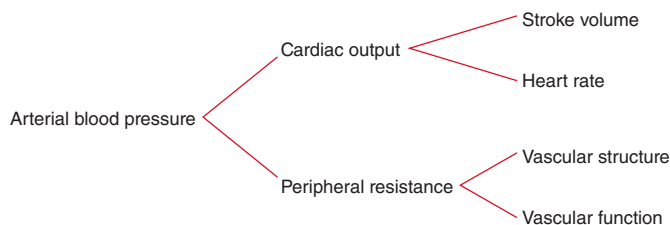


FIGURE 288-1 Schematic depiction of factors that influence the control of blood pressure.

handling, primarily by the kidney, and many neural and hormonal systems that influence peripheral resistance by stimulating vascular constriction (e.g., the sympathetic system and the renin-angiotensin-aldosterone system [RAAS]) or inducing vasodilation (e.g., bradykinin system), and by modulating hormones that result in excretion or retention of sodium (natriuretic peptides and aldosterone, respectively).

Most vascular beds have the capacity to autoregulate blood flow. When peripheral arterial resistance is increased, the autoregulatory systems tend to increase vascular resistance within the vascular bed to maintain constant blood flow. During the 1960s, Arthur Guyton hypothesized that the capacity of the kidney to excrete sodium ultimately dictates long-term changes in levels of BP. Although the Guyton model has been challenged and alternatives proposed, it has had a profound influence on the understanding of BP regulation. A commonly accepted theory is that initial elevation of BP is due to increased cardiac output and expanded intravascular volume; peripheral resistance increases and cardiac output reverts toward normal over time. Whether or not this is the typical sequence of events in the pathogenesis of hypertension, salt can activate a number of neural, endocrine, paracrine, and vascular mechanisms that have the potential to increase arterial pressure. As arterial pressure increases in response to a high intake of sodium chloride, urinary sodium excretion increases, and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this “pressure-natriuresis” phenomenon may involve a subtle increase in glomerular filtration rate (GFR), decreased sodium absorption capacity in the renal tubules, and hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pressure are required to achieve natriuresis and sodium balance.

Many of the drugs used to manage high BP work through influences on the various BP control mechanisms. For example, direct vasodilators and calcium channel blockers (CCBs) work by inducing arteriolar vasodilation. Agents that block the RAAS, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and renin inhibitors, act by blocking the vasoconstricting effects of angiotensin II and sodium-retaining effects of aldosterone. ACEIs also inhibit inactivation of the vasodilator bradykinin, resulting in angioedema in some patients treated with this agent. Beta blockers tend to affect BP by impairing the action of sympathetic system neurotransmitters that stimulate vasoconstriction and heart rate. For example, beta blockers can antagonize the neurotransmitter acetylcholine as well as epinephrine and norepinephrine. In addition to being the most important site for the effect of agents that block the RAAS activity, many drugs affect electrolyte and fluid exchange in the kidneys. Carbonic anhydrase inhibitors have a diuretic effect in the proximal tubules, but due to side effects and diminishing efficacy over time, they are rarely used for BP control. Thiazide and thiazide-like diuretics work to enhance sodium excretion in the distal convoluted tubule and are a mainstay of drug therapy for BP control. They work by reducing intravascular volume, but over the long term, their effect on BP is through reducing peripheral arteriolar resistance. Loop diuretics are more potent diuretics that produce sodium excretion in the loop of Henle. They tend to be relatively short-acting agents that are better suited for sodium excretion than BP reduction. Mineralocorticoid receptor antagonists (MRAs) or aldosterone antagonists are diuretic drugs that work in the distal tubule of the kidney, including the distal convoluted tubule, connecting the tubule and cortical collecting duct, to antagonize the action of aldosterone at mineralocorticoid

2134 receptor sites. These are examples of presumed principal mechanisms of action, but many drugs have other effects on the control of vascular tone and cardiac output that play a role in their effects on BP.

BLOOD PRESSURE MEASUREMENT

Commonly, BP measurements are used to estimate an individual's average level of BP; estimate their risk of CVD, in combination with other indicators; and determine the need for hypertension prevention or treatment. Office and clinic BP measurements are among the most common procedures in clinical practice and arguably provide the best assessment of BP because they have been used in almost all of the landmark BP-CVD risk prediction cohort studies and hypertension prevention and treatment trials. The need for standardization of the BP measurement procedure was recognized by early advocates of BP assessment. Subsequently, the effects of factors that can systematically (predictably) result in falsely high or low BP estimates were quantified, which formed the basis for BP measurement recommendations by professional societies and clinical practice guideline committees. BP also varies randomly (nonpredictably) within and between visits, resulting in corresponding recommendations to rely on an average of repeated readings obtained at more than one visit for classification of an individual's average level of BP. For many years, U.S. clinical practice guidelines have recommended using an average of two or more BP measurements obtained at two or more visits to estimate the usual level of BP. The most important elements for obtaining accurate office BP measurements are visually depicted in Fig. 288-2 and outlined below.

- Instruct the patient to avoid a full bladder and abstain from caffeine, smoking, alcohol, or exercise for 30 min prior to the measurements.
- Use a quiet room with a comfortable ambient temperature.
- Explain the procedure to the patient, including the number of readings.
- Instruct the patient to rest for 3–5 min prior to the first measurement and avoid talking or distractions such as cell phone use during the rest period and subsequent BP measurements.
- Seat the patient in a chair with upright back support. The patient's feet should be flat on the ground and the measurement arm comfortably supported such that the cuff is at heart level.
- Use a clinically validated, preferably automated BP measurement device. Choose a cuff that is the correct size for the patient's arm, and measure their BP at the mid-brachial level.
- The BP measurements should be obtained by a trained, preferably certified, member of the health care team using the arm with the highest pressure at the first visit.

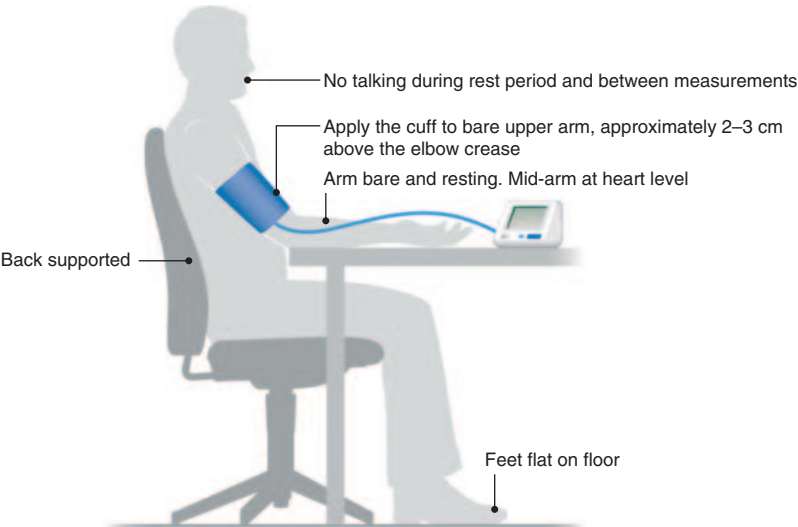


FIGURE 288-2 Schematic depiction of the important elements for accurate measurement of office blood pressure. (Reproduced with permission from AK Cheung et al: International consensus on standardized clinic blood pressure measurement: A call to action. *Am J Med* 136:438, 2023.)

TABLE 288-1 American College of Cardiology/American Heart Association Blood Pressure Classification System in Adults			
BP CATEGORY	SYSTOLIC BP, mmHg		DIASTOLIC BP, mmHg
Normal BP	<120	and	<80
Elevated BP	120–129	and	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90

Abbreviation: BP, blood pressure.

- Use an average of two or more readings at two or more visits to estimate the patient's usual level of BP.
- Provide the patient with the results and an interpretation of their clinical implications.

Most clinical practice guidelines recommend use of a clinically validated oscillometric BP measurement device, a method that eliminates several sources of measurement error and does not require periodic recalibration. Several websites provide a listing of BP measurement devices that have been clinically validated to international standards. These include the Validate BP website in the United States (<https://www.validatebp.org/>) and the STRIDE BP website in Europe (<https://stridebp.org/bp-monitors>). Similarly, many free office and home BP measurement training and certification courses are available, including an easy-to-access course sponsored by the Pan American Health Organization, World Hypertension League, and others (<https://campus.paho.org/en/node/29166>).

DEFINITION OF HYPERTENSION

BP classifications systems differ by country and have changed substantially over time. The current classification proposed by the American College of Cardiology (ACC) and American Heart Association (AHA) for office/clinic BP measurements in U.S. adults is displayed in Table 288-1.

Correct classification presumes accurate BP measurement and averaging of two or more readings obtained at two or more occasions. When the systolic BP (SBP) and diastolic BP (DBP) readings are in different categories of BP, the higher classification should be chosen. In children and adolescents <13 years of age, hypertension is generally based on a comparison with age-, sex-, and height-specific normative data. Hypertension is defined as an average of three SBP or DBP readings at or above the 95th percentile or an SBP or DBP ≥130 or 80 mmHg, respectively. This chapter is focused on BP in adults ≥18 years.

Despite the importance and relative simplicity of accurate BP readings, errors in BP measurement are common in routine clinical practice. Generally, SBP is overestimated by an average of ~7 mmHg, which results in a 15–20% overestimation of hypertension prevalence. However, underestimation of BP and failure to diagnose hypertension are also common. Clinical practice errors vary by level of BP and practice settings and are inconsistent over time, making it impossible to use formulae to correct the errors. For those who aspire to practice evidence-based medicine, the only solution is to follow the recommendations for accurate and precise BP measurements that are advocated by the AHA, ACC, and many other organizations. Having a trained nonphysician staff member obtain routine BP measurements provides an efficient and cost-effective means of obtaining high-quality observations. This is the common practice in research studies and in many large U.S. systems of care.

OUT-OF-OFFICE BLOOD PRESSURE MEASUREMENT

Office BP measurements provide a limited and potentially biased depiction of an individual's usual level of BP. Guidelines commonly recommend complementing office BP readings with out-of-office BP measurements to confirm high office readings and to probe for higher or lower BPs

outside the office. White coat hypertension, in which office BPs meet the criteria for hypertension but out-of-office BPs are nonhypertensive, and masked hypertension, in which office BPs are nonhypertensive but out-of-office BPs meet the criteria for hypertension, are common, with prevalence estimates of 15–25% for both conditions. Adults with white coat hypertension have a CVD risk profile that is more like those without than those with sustained high BPs in and out of the office and they may be best treated with nonpharmacologic interventions, with careful monitoring to recognize a transition to sustained hypertension. In contrast, adults with masked hypertension have a CVD risk profile that is like those with sustained hypertension and may be better treated with a combination of antihypertensive drugs in addition to nonpharmacologic therapy. Masked hypertension should be suspected especially in adults with an elevated but nonhypertensive office BP and evidence of end-organ damage such as left ventricular hypertrophy or proteinuria. Home BP measurements provide the most practical approach to obtaining out-of-office BP readings and provide the additional benefit of engaging patients in their own care. When home BP measurements are desired, patients should be instructed to use a clinically validated BP measurement device and trained to measure their BPs accurately and precisely using the same approaches outlined for measurement of office BPs. Most guidelines recommend using an average of two to three measurements obtained in the morning (before taking antihypertensive medications) and evening. In the United States, obtaining home BP measurements for about 3 days prior to an office visit represents a reasonable and practical option for estimating a patient's usual level of home BP. The BP for recognition of hypertension is the same for office and home BP measurements (SBP ≥ 130 and DBP ≥ 80 mmHg). Likewise, the BP control is defined as an SBP/DBP $< 130/80$ mmHg in both settings. Many home BP measurement devices allow for storage of the readings on a memory chip and for transfer to the physician's office by use of telemetry. This approach thwarts the potential for the bias of more favorable readings that can occur with written patient self-reports. Ambulatory BP measurements are best obtained by practitioners with special expertise in this technique and interpretation of the results. The equivalent SBP/DBP readings for an office average of 130/80 mmHg are 130/80, 110/65, and 125/75 mmHg for daytime, nighttime, and 24-h ambulatory readings, respectively. Ambulatory BP measurements provide the potential for scrutiny of nighttime readings, which may provide the best BP prediction of CVD risk. Specifically, those whose BPs fail to follow the usual pattern of a pronounced decrement during the nighttime (nondippers) tend to have a higher risk of CVD. BP nondipping is more common in non-Hispanic blacks than the other major racial/ethnic groups in the United States. Ambulatory BP measurement is relatively expensive and intrusive. Patients in the United States are usually reluctant to undergo repeat ambulatory BP measurements, making this measurement method most useful in confirming the diagnosis of hypertension, especially where uncertainty is a special concern. Wearable devices, including watches, hold great promise for the provision of convenient ways to obtain a more comprehensive assessment of daytime and nighttime BPs, but none of the currently available options are clinically valid.

PREVALENCE OF HYPERTENSION

Prevalence estimates vary depending on the criteria for definition of hypertension, the methods for BP measurement, and the population being studied; hypertension is very common, especially at older age. Age-related increases in BP are noted in almost all countries. Generally, SBP increases progressively until about the eighth decade of life. DBP also increases with age, but less steeply than SBP, until about the fifth decade of life and remains stable or declines thereafter. Isolated systolic hypertension is common late in life due to a widening of the pulse pressure (difference between SBP and DBP). Generally, those who have the highest or lowest BPs early in life tend to “track” in the same extremes of BP over life, with high pressures early in life providing a crude opportunity to identify those at higher risk for hypertension in adulthood. Little or no age-related change in BP has been observed in many isolated populations and in subsets of populations in countries where age-related increases in BP are common. This

observation indicates that there is no biological necessity for the commonly observed age-related increase in BP and underscores the value of interventions aimed at prevention of hypertension. Migrant studies that have tracked isolated populations from their native environment to nonnative settings have uniformly reported progression to the more common pattern of age-related increases in BP. These BP changes have been associated with increases in dietary sodium and decreases in potassium intake, consumption of a less healthy diet, decreased physical activity, increases in body weight, and increased intake of alcohol.

Based on the ACC/AHA criteria for diagnosis, >103 million adults in the United States have hypertension, making it one of the most common health conditions reported. Hypertension is present in ~20–30% of U.S. adults aged 20–44 years, but the prevalence increases to 80–85% in those aged 75 years or older. The overall prevalence of hypertension in U.S. adults has remained fairly stable in recent decades (~46% overall). Men have slightly higher BPs compared to women during the first half of life, but the opposite is true in later life. In the United States, non-Hispanic black adults have a prevalence of hypertension (59%) that is substantially higher compared to whites (45%), Hispanics (47%), or Asians (46%). Adjusted estimates of hypertension in adult non-Hispanic black men and women are reported to be 59 and 56%, respectively, whereas the corresponding estimates for non-Hispanic white men and women are 47 and 41%, respectively. In addition, hypertension in non-Hispanic black adults tends to begin at a younger age and result in more CVD and kidney complications compared to the other major racial/ethnic groups in the United States. The prevalence of hypertension and CVD complications (especially stroke) is higher in the southeastern United States compared to other regions of the country, especially the northwest. No matter how defined, hypertension is very common in all parts of the world, with a progressively increasing prevalence in low- and middle-income countries and a slight decline in high-income countries. Using the hypertension definition of SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication, the prevalence in adults was estimated to be 31.5% (1.04 billion) in low- and middle-income countries and 28.5% (349 million) in high-income countries in 2010. As in the United States, hypertension prevalence is very age-dependent and varies by region, race/ethnicity, and other factors, including importantly socioeconomic factors, in most countries.

LABORATORY AND OTHER INVESTIGATIONS

In patients with newly diagnosed hypertension, basic laboratory testing is indicated to (1) recognize the presence and extent of target organ damage; (2) facilitate the identification of secondary causes of hypertension, including kidney disease and primary aldosteronism; (3) recognize comorbid conditions, including diabetes mellitus and hyperlipidemia; (4) estimate atherosclerotic CVD (ASCVD) risk in patients without a history of a CVD; and (5) assist in the optimal choice of antihypertensive drug therapy. At a minimum, a complete blood count, serum electrolytes (sodium, potassium, calcium), serum creatinine and estimated GFR (eGFR), lipid profile, glycemic status (hemoglobin A_{1c} or fasting blood glucose), thyroid-stimulating hormone level, urinalysis and urine albumin-to-creatinine ratio, and 12-lead electrocardiogram (ECG) should be obtained. These basic tests can be complemented by other evaluations as clinically indicated. In some countries, it is not possible to obtain the minimally recommended laboratory results. Guidelines written for clinicians in such countries, including the 2021 World Health Organization (WHO) guideline for the treatment of hypertension in adults, recommend that this should not be an impediment to BP reduction.

ESTIMATION OF CARDIOVASCULAR DISEASE RISK

Abundant studies have shown that BP is associated with CVD risk in a continuous, progressive, log-linear fashion from low to high levels of SBP and DBP. For SBP, the risk relationship has been documented from as low as 90 mmHg to more than 180 mmHg, suggesting relatively low levels of BP, if physiological, may be optimal to prevent the genesis of BP-related atherosclerotic complications. It also suggests that

one might reasonably expect a “lower BP is better” finding in antihypertensive randomized controlled treatment (RCT) trials. In addition to CVD, the level of BP is strongly associated with other diseases, including CKD, ESKD, and dementia. The BP-CVD risk association in observational studies is equally true for men and women. The BP-related slope for relative risk of CVD is steeper at younger age when BP elevation is often an isolated risk predictor. In older adults, the corresponding slope for CVD risk is less steep, but the absolute risk of CVD is far higher because other CVD risk factors are common in those with an elevated BP. At any level of BP, the risk of a CVD complication varies dramatically with more than a 30-fold difference in 10-year predicted risk of CVD for those with an isolated elevation of BP compared to their counterparts with multiple CVD risk factors in addition to an elevated BP. This observation has special relevance for clinical decision-making in patients with a usual SBP between 130 and 139 mmHg. In individuals with stage 1 hypertension as an isolated CVD risk factor, the 5- or 10-year risk of a CVD event may be quite small and limit enthusiasm for introducing antihypertensive drug therapy. However, when stage 1 hypertension is accompanied by other CVD risk factors, the corresponding risk of ASCVD may be quite high and make prescription of antihypertensive drug therapy much more appealing. In antihypertensive clinical trials, the relative risk reductions for CVD events are similar in groups with different levels of underlying CVD risk, but the absolute benefit is much greater in the groups at higher risk for ASCVD. For both these reasons, CVD risk assessment should be part of the initial evaluation.

Patients with a history of a prior CVD complication are known to be at high risk for recurrent CVD events. In those without a history of prior CVD, ASCVD risk should be estimated using a risk calculator. For U.S. adults 40–75 years of age, use of the ACC/AHA pooled cohort equations estimator is recommended because it has been validated in non-Hispanic white and black adults. Those with a 10-year risk of ASCVD $\geq 10\%$ should be considered at high risk. PREVENT is an updated risk predicting model that is based on a larger and more current dataset than that used for the pooled cohort equations model. It incorporates an assessment of kidney (glomerular) function and allows for inclusion of urinary albumin/creatinine ratio, zip code for assessment of the social determinants of health, and hemoglobin A_{1c} where indicated and has been introduced by the AHA as a replacement for the pooled cohort equations. It can be used in U.S. adults aged 30–70 years to predict 10- and 30-year CVD risk. It includes the prediction of heart failure risk, an important feature in the care of patients with hypertension. Over time, the PREVENT instrument is expected to replace the current pooled cohort equations risk prediction model.

CAUSES OF HYPERTENSION

■ PRIMARY HYPERTENSION

Most adults have “primary” hypertension, with no obvious underlying anatomic cause of their high BP. Adoption, twin, clinical, and family studies provide evidence for a heritable component of high BP and hypertension. However, much of this may be due to a shared environment because, with rare exceptions, genetic investigations have only identified modest polygenic associations between multiple genes and BP. While genetic research remains an important area for investigation, the clinical implications of genetic studies for diagnosis and management of high BP are currently very limited.

Strong associations with level of BP have been reported for several general environmental exposures, including heavy metals such as lead, mercury, cadmium, and arsenic. Several indicators of air pollution, commonly including levels of particulate matter with a diameter of 2.5 microns (PM_{2.5}) or less, have been associated with higher levels of SBP and DBP. In most studies, the increase in SBP has been ~3–5 mmHg, but the magnitude can vary depending on quantity and duration of the exposure. Air pollution is a challenge worldwide, but the level of exposure to pollutants varies widely by geography, climate, season, and extent of economic development. In addition to air pollution, clinically important changes in BP are recognized in geographic regions that experience large seasonal variations in ambient

temperature, with lower and higher BPs during the warmest and coldest seasons, respectively. BP also tends to be higher in those who are acutely exposed to high altitudes, possibly due to a combination of hypoxia and cold temperatures.

Personal environmental exposures related to components of diet, physical activity, and alcohol consumption seem to be responsible for much of the age-related increases in BP that are common in most countries. A large body of ecological, migrant, and longitudinal cohort studies have documented higher BPs in those who consume unhealthy diets, have an excessive intake of sodium or an inadequate intake of potassium, are physically inactive, are overweight or obese, or consume alcohol. Many of these exposures have also been linked to CVD complications. For example, insufficient dietary intake of potassium has been identified as a risk factor for stroke in many studies. Stress and other psychosocial indicators have also been associated with higher BPs and CVD events. The six personal exposures identified in [Table 288-2](#) (diet quality, body weight, excessive dietary sodium intake, insufficient dietary potassium intake, physical inactivity, and alcohol consumption) are all highly prevalent and strongly associated with higher BP and age-related increases in BP. About half of U.S. adults report attempts to eat a heart healthy diet, but this is likely to represent an overestimate. Almost all adults worldwide exceed the intake of dietary sodium and fail to meet the level of dietary potassium recommended by the WHO and national organizations. Likewise, excess body weight is very common in many countries. For example, approximately three-quarters of U.S. adults are either overweight (body mass index [BMI] 25–29 kg/m²) or obese (BMI ≥ 30 kg/m²). More than a quarter of U.S. adults report no physical activity outside their workplace, and about half report less than the recommended level of physical activity (≥ 150 min of aerobic exercise/week). About 85% of U.S. adults report consumption of alcohol at some point during their life, with >60% reporting alcohol consumption during the previous year and 25% reporting binge drinking during the previous month. Thus, these six exposures are not only closely related to level of BP and targets for interventions aimed at BP lowering but also extremely common exposures.

■ SECONDARY HYPERTENSION

A minority of patients have “secondary” hypertension, with an overt underlying anatomic or biochemical cause for their high BP. Secondary hypertension should be considered during the evaluation of all patients with new-onset hypertension and in selected patients with prevalent hypertension who have indicators that suggest the possibility of a complicating secondary cause of hypertension, including (1) treatment-resistant hypertension; (2) abrupt worsening of hypertension; (3) disproportionate target organ damage for level of BP; and (4) laboratory or diagnostic findings such as unprovoked hypokalemia, proteinuria, or left ventricular hypertrophy. The approximate prevalence, pathophysiology, possible clinical and physical examination findings, common screening and confirmatory tests, and potential treatments for the six most common causes of secondary hypertension are summarized in [Table 288-3](#).

Obstructive Sleep Apnea Obstructive sleep apnea (OSA) is probably the most common cause of secondary hypertension. It is closely associated with overweight, obesity, and other comorbidities. The reported prevalence of OSA varies substantially depending on the criteria used for definition and methods of ascertainment. However, it is very common and may be present in as many as 15–30% of adult men and 10–15% of adult women in the United States. More than half of U.S. adults with OSA have hypertension and >30% of U.S. adults with hypertension have OSA. OSA and hypertension share many common pathophysiologic features, including being overweight, obesity, unhealthy lifestyles, and abnormalities of the renin-angiotensin system and fluid distribution. Sympathetic system activation due to intermittent hypoxia is also an important component of the underlying pathophysiology in OSA. Almost three-quarters of patients with OSA are overweight or obese. In general, there is a direct association between the severity of OSA and an individual's level of BP as well as their resistance to antihypertensive therapy. Resistant hypertension,

TABLE 288-2 Summary Information for the Six Best Proven Nonpharmacologic Interventions That Lower Blood Pressure

CHARACTERISTIC	BP ASSOCIATION	INTERVENTION	REGIMEN	EXPECTED CHANGE IN BP
Diet	BPs are lower in those who consume heart-healthy diets.	Consumption of a heart-healthy diet, especially the Dietary Approaches to Stop Hypertension (DASH) diet.	DASH diet meal plans are readily available.	With good adherence to the DASH diet plan, an average SBP reduction of about 5 mmHg can be expected in patients with and 2–3 mmHg in those without hypertension.
Body weight	Increased body weight is directly associated with SBP/DBP. Almost 75% of U.S. adults are overweight (BMI 25–<30 kg/m ² ; 31%) or obese (BMI ≥30 kg/m ² ; 42%).	In most patients, weight loss should be achieved by behavioral counseling. In a minority, drug therapy should be considered. Bariatric surgery should be confined to adults with a BMI ≥40 kg/m ² or ≥35 kg/m ² and hypertension or another obesity-related comorbidity.	Behavioral interventions are aimed at a combination of calorie reduction and increased physical activity.	Generally, SBP is reduced by ~1 mmHg for every kilogram reduction in body weight. In high-quality RCTs, an average reduction of about 10 lb (4.5 kg) has been common at 6–12 months.
Sodium intake	Dietary sodium is directly associated with SBP, and excessive intake may be important in age-related increases in BP.	Behavioral counseling, use of salt substitutes, public health messaging, and policy to reduce the amount of sodium added during food processing and commercial preparation.	The sodium-BP dose response is almost linear, so any reduction in sodium intake is beneficial. Optimal target recommendations vary from <1500 to 2300 mg sodium intake per day.	In high-quality behavior change trials, average sodium intake is reduced by ~25% and SBP by ~5 mmHg and 2–3 mmHg for adults with and without hypertension, respectively. Use of salt substitutes has resulted in prevention of stroke (14%), CVD (13%), and all-cause mortality (12%) in addition to BP lowering.
Potassium intake	Potassium intake is inversely associated with BP and a lower risk of CVD, especially stroke.	Dietary or pill supplementation, but the former is preferred. An additional intake of 2000 mg/d (~50 mmol/d).	The recommended intake of potassium in adults is ~3500 mg/d. A dose-response meta-analysis suggests supplementing usual intake by ~1200 mg/d may be optimal. Potassium supplementation is contraindicated in patients with hyperkalemia or advanced kidney disease or who are taking medicines that increase the risk of hyperkalemia.	Clinical trial meta-analyses have repeatedly shown that potassium supplementation by diet or pill use lowers BP. The average reduction in SBP has been ~5 and 3 mmHg in adults with and without hypertension, respectively. Greater reductions are observed in adult black patients and those consuming large amounts of dietary sodium.
Physical activity	Observational studies identify a strong inverse association between physical activity and BP, hypertension, and CVD.	Aerobic, dynamic resistance, and isometric resistance exercises.	Most trials have evaluated aerobic exercise interventions, and this type of exercise is commonly prescribed. Most guidelines recommend ≥150 min of aerobic exercise per week. However, any increase in physical activity and any type of exercise are likely to be beneficial.	In adults with hypertension, aerobic exercise is likely to reduce SBP by ~5 mmHg and, when combined with dynamic resistance exercise, by ~7 mmHg. The extent of BP lowering depends on the starting level of BP and success of the intervention.
Alcohol consumption	Alcohol intake is associated with BP and hypertension in a direct and roughly linear fashion, with no threshold for the association.	Most commonly, substitution of lower alcoholic or nonalcoholic beverages, but behavioral counseling and abstinence, without access to alcohol, have been used in some trials.	Most interventions have targeted a reduction in alcohol consumption, often to ≤2 and ≤1 standard drinks per day in men and women, respectively. However, any reduction in alcohol consumption is helpful.	The extent of BP lowering depends on the starting level of alcohol consumption and the magnitude of the reduction in alcohol intake. Commonly, alcohol reduction trials have resulted in an SBP reduction of >5 mmHg in adults with hypertension.

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic BP; RCT, randomized controlled trials; SBP, systolic BP.

snoring, poor quality sleep, breathing pauses during sleep, and daytime sleepiness are common clinical indicators of OSA. Several simple questionnaire-based tests are available to screen for those who should be evaluated more carefully with a sleep study (polysomnography). Lifestyle improvements, especially those resulting in weight loss, are an important component of treatment for both OSA and any associated hypertension. OSA-specific treatment includes continuous positive airway pressure (CPAP), but meta-analyses demonstrate limited BP lowering due to CPAP treatment. As a result, hypertension in patients with OSA should be treated with antihypertensive drug therapy in addition to nonpharmacologic therapy.

Medication and Other Substances Prescription and over-the-counter medications, herbal and food additives, and illegal substances are often identified as secondary causes of new-onset hypertension or diminished BP control in patients being treated for hypertension. Typically, the increase in BP results from a direct pressor effect of the agents, but these exposures can also have an indirect effect on

BP as a result of drug-drug or drug-nondrug exposure interactions. Some of the most common prescription drugs that can increase BP include amphetamines, angiogenesis inhibitors, antidepressants and antipsychotic agents, decongestants, oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic corticosteroids. Examples of illicit drugs that can result in a higher BP include cocaine, marijuana, amphetamines, and methylenedioxymethamphetamine. Herbal treatments that have been reported to raise BP include arnica, ephedra (Ma-Huang), ginseng, guarana, consumption of large quantities of licorice, and St. John's wort. Finally, caffeine and several anesthetic agents can result in short-term elevation of BP. A careful history will identify most of these agents and will allow for use of alternatives or a reduced dosage in most patients. The exact prevalence of exposure to any of these agents is uncertain but high. For example, in the nationally representative 1999–2004 National Health and Nutrition Examination Survey (NHANES), >26% of U.S. adults reported regular NSAID use, and the percentage was much higher in older adults and in non-Hispanic whites.

TABLE 288-3 Summary Description of the Most Common Secondary Causes of Hypertension

CAUSE	PREVALENCE	PATHOPHYSIOLOGY	CLINICAL INDICATORS	PHYSICAL EXAMINATION	SCREENING TESTS	CONFIRMATORY TESTS	TREATMENT
Obstructive sleep apnea (OSA)	OSA is very common (10–30% of U.S. adults). More than 50% of U.S. adults with OSA have hypertension, and ~30% with hypertension have OSA.	OSA and hypertension share many common pathophysiologic features, including overweight and obesity. Activation of the sympathetic system due to intermittent hypoxia is an important component of the pathophysiology for OSA.	Resistant hypertension, snoring, poor quality sleep, breathing pauses during sleep, daytime sleepiness, overweight and obesity	Obesity and signs of upper airway narrowing	OSA screening questionnaires (several have been validated)	Polysomnography (sleep study)	Lifestyle improvement, especially aimed at weight loss, is indicated for both OSA and associated hypertension. Antihypertensive drug therapy. Continuous positive airway pressure (CPAP) treatment for OSA has little effect on BP.
Medication and other substances	High prevalence. Numerous potential exposures. For NSAID alone, >26% of U.S. adults reporting regular use.	Varies depending on exposure.	Usually exposure best detected by medical history report	Occasionally, specific physical exam findings, e.g., signs suggesting cocaine use	History taking	History taking	Discontinuation, substitution of alternative therapy, or maintenance of exposure but management of high BP.
Renal parenchymal disease.	One of the most common causes of secondary hypertension (>5%).	Various kidney diseases, including polycystic renal disease, chronic glomerulonephritis, diabetic and hypertensive kidney disease, recurrent stones, and kidney infections.	Resistant hypertension, fatigue, edema, report of hematuria	Proteinuria, renal mass	Serum creatinine, albuminuria, glucose abnormality	Imaging by sonography, CT, or MRI Renal biopsy	Treatment of ASCVD risk factors, including hypertension. Management of the specific kidney disease, if feasible.
Primary aldosteronism	One of the more common causes of secondary hypertension, responsible for the high BP in ~5% of adults with hypertension.	Idiopathic bilateral adrenal hyperplasia (60–70%) Benign adrenal adenoma (30–40%) Occasionally, familial Rarely due to other causes	Severe or resistant hypertension Hypokalemia Nonspecific fatigue, muscle cramps, or weakness Incidental finding of adrenal adenoma Obstructive sleep apnea Family history of early-onset hypertension or stroke	No specific findings on clinical examination	High plasma aldosterone/renin ratio, when measured under standardized conditions CT of the abdomen	Saline suppression test or captopril challenge test are helpful, but adrenal vein sampling for aldosterone levels is generally accepted as the gold standard test.	Adrenalectomy (laparoscopic or surgical) for many patients with an adrenal adenoma. Hypertension due to adrenal hyperplasia best treated medically, with inclusion of a mineralocorticoid receptor antagonist, and lifestyle changes to reduce sodium intake and body weight.
Renovascular disease	Generally reported to approximate 5%.	Usually unilateral disease due to ASCVD (90%) with >70% arterial lumen narrowing. About 10% due to fibromuscular disease, typically occurring in middle-aged white women.	Early, abrupt-onset hypertension (consider fibromuscular disease) Rapidly worsening or resistant hypertension in older adults (consider ASCVD)	Bruits, especially abdominal renal artery bruit	Various imaging options, including Doppler ultrasonography, magnetic resonance, or CT angiography	Digital subtraction angiography	PTA may cure or substantially improve hypertension in patients with discrete fibromuscular disease lesions. Medical treatment is preferred in patients with ASCVD and those with very diffuse fibromuscular disease.
Hypertensive disorders of pregnancy	During pregnancy, approximate prevalence of hypertension 10%, preeclampsia 3%, and eclampsia 0.1–0.3%.	Varies depending on whether the hypertension is new onset or chronic. New-onset hypertension seems to result from reduced placental perfusion and subsequent elevation in peripheral resistance, which usually disappears after delivery.	High BP Preeclampsia if high BP is accompanied by proteinuria or other evidence of target organ damage	High BP, with or without proteinuria	No specific screening tests	Diagnosis by recognition of high BP, based on an average of ≥2 accurately measured BP readings taken on ≥2 occasions	Lifestyle counseling and antihypertensive medication. ACEIs and ARBs should not be used. Initial use of the β-blocker labetalol and/or the CCB nifedipine is commonly recommended because of their safety record and known efficacy in pregnancy.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CT, computed tomography; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PTA, percutaneous transluminal angioplasty.

Renal Parenchymal Disease This is also relatively common and probably accounts for >5% of all non-OSA and medication-related secondary causes of hypertension. It can result from almost any type of underlying kidney disease but is somewhat more common with glomerular than interstitial disorders. Most patients with CKD disease have hypertension. Importantly, it is often difficult to determine the extent to which a patient's high BP is the cause or a consequence of their kidney disease. Activation of the RAAS is often a part of the underlying pathophysiology that leads to hypertension. Clinical indicators of hypertension due to renal parenchymal disease include treatment resistance, fatigue, palpation of a renal mass, hematuria, proteinuria, elevated creatinine, or hyperglycemia. Imaging with sonography, computed tomography (CT), or magnetic resonance imaging (MRI) can be helpful for the diagnosis of some forms of underlying kidney disease. Renal biopsy is most helpful when glomerulonephritis is suspected. Most patients with CKD have a variety of both conventional and novel risk factors for ASCVD placing them at high risk for CVD complications. Improvement of CVD risk factors, including hypertension, is an essential element of treating patients with CKD. Often, control of hypertension may require use of three or more antihypertensive agents in addition to lifestyle management. Diuretics and RAAS inhibitors such as ACEIs and ARBs are obvious components of the antihypertensive drug treatment regimen. Traditionally, thiazide and thiazide-like diuretics were thought to be relatively ineffective for the management of patients with a serum creatinine >3 mg/dL, but a recent well-conducted trial documented substantial BP and albuminuria reduction in patients with advanced CKD who were treated with the long-acting diuretic chlorthalidone. Finerenone, a newer MRA, has also been shown to enhance BP reduction in patients with advanced CKD. Gliflozins or sodium-glucose cotransporter 2 (SGLT2 inhibitors), which are often very useful in the management of patients with CKD, are diuretics and may provide a small reduction in BP. If possible, the underlying kidney disease should be treated with specific therapy.

Primary Aldosteronism A relatively common cause of secondary hypertension, primary aldosteronism may be the underlying cause of high BP in ~5% of adults with non-OSA and medication-related secondary hypertension. However, the reported prevalence varies widely depending on the criteria for diagnosis and the population studied. Most patients with primary aldosteronism (60–70%) have idiopathic bilateral adrenal hyperplasia but ~30–40% have a benign adenoma, usually unilateral. Often, the clinical presentation is subtle with no more than resistant hypertension or nonspecific symptoms. However, in some patients with more pronounced aldosteronism, unprovoked hypokalemia or hypokalemia-related cardiac arrhythmias, such as atrial fibrillation, may be present. Common screening tests for primary aldosteronism include abdominal imaging by CT to detect an adenoma and measurement, under standardized conditions, of a high aldosterone/renin ratio in conjunction with high plasma aldosterone levels. Several noninvasive investigations, including the saline suppression and captopril challenge tests, can provide more definitive evidence of primary aldosteronism, but adrenal vein aldosterone sampling is generally accepted as the gold standard test for diagnosis. The most important goal is to recognize the minority of patients with a benign unilateral adenoma whose hypertension can be cured or substantially improved by adrenalectomy. The latter can be accomplished by minimally invasive laparoscopy or by use of traditional surgical techniques. Medical management of hypertension in patients with aldosteronism should include the use of MRA agents. In most patients, spironolactone is well tolerated but occasionally adverse effects, including hyperkalemia, breast tenderness, or gynecomastia in men, require the substitution of newer, more expensive, alternative MRAs. The screening tests and especially the more definitive diagnostic tests for primary aldosteronism require careful attention to detail and are generally best conducted by those who have specialized experience in the evaluation of patients who may have primary aldosteronism. Likewise, most adrenal adenomas are very small, and removal by laparoscopy or surgery is most successful when performed by an experienced treatment team.

Rarely, primary aldosteronism can be caused by an adrenal carcinoma, ectopic malignancy, or rare genetic disorders.

Renovascular Hypertension Renovascular obstructions that result in substantial and hemodynamically important occlusion of the renal artery can result in hypertension and impaired renal function. Renovascular disease is found in as many as 25% of patients at autopsy, but renovascular hypertension only accounts for ~1% of the high BP in all patients with hypertension. In ~90% of patients with renovascular hypertension, renal artery obstruction is caused by atherosclerosis. Commonly, atherosclerotic renovascular disease is unilateral and the principal obstruction tends to present as a discrete lesion found close to the origin of the renal artery. Patients with atherosclerotic renovascular disease tend to be older and have other indications of ASCVD, including an abnormal risk factor profile and atherothrombotic lesions in other vascular beds. At times, a bruit can be heard over the renal artery or over the carotid or femoral arteries. A minority of patients with renovascular disease have fibromuscular disease. They tend to be younger, mostly white, women. Their renal artery lesions are more diffuse, with an irregular sawtooth appearance, and they are frequently located in more distal parts of the renal artery compared with atherosclerotic lesions. In addition, bilateral renal artery disease is more common in patients with fibromuscular disease than is the case for renovascular disease due to ASCVD. Fibromuscular disease should be suspected in any patient with abrupt-onset hypertension, especially in young white women, and in those with resistant hypertension, or recent worsening of hypertension. Underlying atherosclerosis should be suspected in older patients with other indications of ASCVD and in those with otherwise unexplained worsening of kidney function. The threshold for additional diagnostic investigations should be lower when fibromuscular disease is suspected.

A variety of screening tests, including renal ultrasound studies, CT and magnetic resonance angiography imaging studies, renograms, and standardized measurement of plasma renin activity, can be used to exclude other causes of hypertension and to screen for evidence of renovascular disease. Renal angiography provides more definitive evidence of the extent and type of renovascular disease and is currently considered to be the gold standard diagnostic test. Skilled interventional radiologists can employ digital subtraction angiography to generate high-quality studies with less contrast exposure compared to standard angiography. Hypertension due to renovascular disease is more likely in patients with lesions that occlude >70% of the vessel lumen. For many years, renal venous renin sampling was a gold standard diagnostic test but is now rarely performed due to a high frequency of false-positive and false-negative results.

In many patients with hypertension due to fibromuscular disease, percutaneous transluminal angioplasty results in a cure for their hypertension or substantially improves the control of their high BP. For this reason, the most important goal in evaluating patients with suspected renovascular hypertension is to recognize individuals with underlying fibromuscular disease. As is the case for some other forms of secondary hypertension, screening, diagnosis, and treatment results tend to be better when conducted by teams with experience in caring for patients with renovascular disease. Several well-conducted randomized controlled trials, with relatively large sample sizes, have failed to demonstrate any special benefit for BP control or renal preservation following percutaneous transluminal angioplasty or renovascular surgery compared to medical care in patients with atherosclerotic renovascular hypertension. Most patients with suspected atherosclerotic renovascular hypertension should be managed using a combination of nonpharmacologic and antihypertensive drug therapy, including the use of agents that block the RAAS. In rare instances, arteritis and other inflammatory disease can be the underlying cause of renovascular hypertension. The underlying cause should be treated in addition to medical management of hypertension.

Hypertensive Disorders of Pregnancy Hypertension occurs in >10% of pregnancies in the United States and about 3–5% are complicated by preeclampsia, in which hypertension is accompanied by proteinuria or other evidence of target organ damage. The HELLP

syndrome, in which hypertension is accompanied by hemolysis, elevated liver enzymes, and low platelets, represents a more severe form of preeclampsia. Progression to eclampsia, with seizures as the cardinal feature, occurs in <1% of women with mild and about 3% of those with severe preeclampsia. Hypertension during pregnancy is associated with a higher rate of fetal complications and of hypertension and CVD complications for the mother later in life. Hypertensive disorders of pregnancy include the following: (1) chronic hypertension, in which the high BP precedes pregnancy; (2) gestational hypertension, in which new-onset hypertension is recognized after 20 weeks of gestation; (3) preeclampsia potentially culminating in eclampsia; and (4) chronic hypertension with superimposed preeclampsia. Management of hypertension in pregnancy often includes bed rest, nonpharmacological interventions, and pharmacotherapy. Clinical trials and meta-analyses provide strong evidence that antihypertensive therapy during pregnancy reduces the risk of progression to more severe hypertension, compared to placebo, but less convincing evidence for prevention of preeclampsia and other fetal complications. ACEI and ARB therapy should be avoided due to the potential for teratogenic side effects. Few high-quality studies have compared the benefits and risks of treatment with other commonly used antihypertensive drugs during pregnancy. Usually, treatment with the beta blocker labetalol, the CCB nifedipine, or the centrally acting α_2 -adrenergic agonist methyldopa is recommended as providing safe first-line antihypertensive drug therapy, with one trial suggesting that labetalol and nifedipine may be superior to methyldopa for prevention of preeclampsia. A review of prescribing habits in the United States identified labetalol, nifedipine, and the direct vasodilator hydralazine as the three most commonly used antihypertensive agents during pregnancy. Clinical trials have failed to demonstrate a benefit for more intensive therapy to a SBP/DBP <130/80 mmHg compared to <140/90 mmHg.

Less Common Causes of Secondary Hypertension There are many other secondary causes of hypertension, but they tend to be infrequent and are generally best considered when patients are referred to consultants with expertise in recognizing rare causes of secondary hypertension. These include Cushing's syndrome in which large amounts of cortisol are produced in response to excessive levels of adrenocorticotrophic hormone (ACTH) produced by a pituitary gland adenoma or ectopic ACTH-producing tumor, an adrenal adenoma, or treatment with glucocorticoids. Clinical signs of note include weight gain in the face (moon face) and trunk, a fatty lump between the shoulders (buffalo hump), thin arms and legs, pink or purple stretch marks on the stomach, hips, thighs, breasts, and underarms, easy bruising, slow healing, and acne. Screening and diagnosis are usually based on an assessment of 24-h urinary corticosteroid levels, imaging tests, and an overnight dexamethasone-suppression test. More than 75% of patients with Cushing's syndrome have hypertension. Treatment depends on the underlying cause of the syndrome. *Pheochromocytoma* is another rare form of secondary hypertension and is caused by excessive production of catecholamines, usually due to a benign neuroendocrine tumor composed of chromaffin cells located in the adrenal medulla (80–85%) or in extra-adrenal paraganglion tissue (paraganglioma). Most patients with pheochromocytoma present with hypertension at a relatively young age (often 30–50 years). Many have nonspecific signs and symptoms, but some have paroxysmal attacks characterized by high BP, sweating, headaches, and cardiac arrhythmias. Screening and diagnosis are usually based on blood and 24-h urinary catecholamine values and abdominal CT, MRI, or positron emission tomography imaging studies. Typically, pheochromocytomas are treated by complete or partial adrenalectomy using minimally invasive surgical techniques. A small minority of patients with pheochromocytoma have an inherited genetic predisposition such as multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Landau disease, neurofibromatosis, and hereditary paraganglioma syndromes. Coarctation of the aorta is the most common congenital cause of hypertension and results from a birth defect in which a portion of the aorta is narrower than usual. When the defect is severe, the coarctation is likely to be detected early in life and may be associated with other

congenital abnormalities. When the defect is mild, the disorder may not be recognized until early adulthood. The classical physical examination findings are delayed and diminished femoral and distal pulses. A systolic murmur may be heard in the posterior intrascapular area, and signs of left ventricular hypertrophy may be detected. Screening and diagnostic tests include imaging studies such as echocardiography, CT, and angiography. Treatment options include balloon angioplasty, surgery, and medical management. Other rare causes of hypertension include hyper- and hypothyroidism, acromegaly, and hypercalcemia.

PREVENTION AND TREATMENT OF PRIMARY HYPERTENSION

Both nonpharmacologic interventions, mostly lifestyle improvements, and antihypertensive medication play a role in the management of high BP.

The overall approach to prevention and treatment of hypertension, which is depicted in [Fig. 288-3](#), is to encourage a healthy lifestyle in adults with a normal BP (SBP/DBP <120/80 mmHg) and actively advise nonpharmacologic therapy in adults with an elevated BP (SBP 120–129 mmHg and DBP <80 mmHg). Adults with stage 2 hypertension (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg) should be treated with a combination of nonpharmacologic and antihypertensive drug therapy. Most adults with stage 1 hypertension (SBP 130–139 mmHg or DBP 80–89 mmHg) should be managed by active application of nonpharmacologic interventions, but in the minority (~30% in the United States) who have a history of CVD or are at high risk for ASCVD, antihypertensive medication should be added to the nondrug approaches to lower BP. In RCTs, low-dose pharmacotherapy has been effective for BP lowering, prevention of hypertension, regression of left ventricular mass, and prevention of left ventricular hypertrophy in nonhypertensive patients. However, drug therapy is not recommended for this purpose in any major clinical practice guideline. The next two sections provide a more detailed guide to the selection and application of nonpharmacologic and antihypertensive drug treatments.

■ NONPHARMACOLOGICAL INTERVENTIONS TO PREVENT AND TREAT HYPERTENSION

Many nondrug interventions have been reported to lower BP. Most of them are based on changing personal exposures associated with higher BP. The best proven approaches to nonpharmacologic lowering of BP are displayed in [Table 288-2](#).

Generally, the nonpharmacologic interventions used in clinical practice settings require a change in behavior. However, pill supplementation to enhance potassium intake, renal denervation therapy in selected patients with resistant hypertension, and baroreceptor activation therapy are examples of nonpharmacologic treatments that are not primarily based on achieving behavior change. For the nonpharmacologic interventions based on behavior modification, the difficulty of achieving the desired changes varies by intervention and patient, but generally, behavior change can be hard to achieve and maintain over long periods of time. Behavior change interventions are most successful when patients accept the need for change, pledge to embrace the behavioral changes that are necessary, and can be counseled by a member of the health care team who is knowledgeable in the techniques for behavior change. For weight loss, abstinence from alcohol, physical activity, and high-quality counseling programs that are available in convenient locations close to a patient's home or workplace may provide an alternative option to office/clinic-based counseling. Behavior change can be successful in any patient but is especially likely in those with or at high risk for CVD and in patients who have the time, resources, and desire to concentrate on improving their health behaviors. Not surprisingly, older adults and those with higher socioeconomic status (SES) tend to be more successful than their younger and lower SES counterparts. The following are brief summaries of specific aspects of the six interventions identified in [Table 288-2](#).

Diet Quality Heart healthy diets tend to lower BP and improve other diet-related CVD risk factors, such as low-density lipoprotein cholesterol and blood glucose. For example, a reduction in BP has

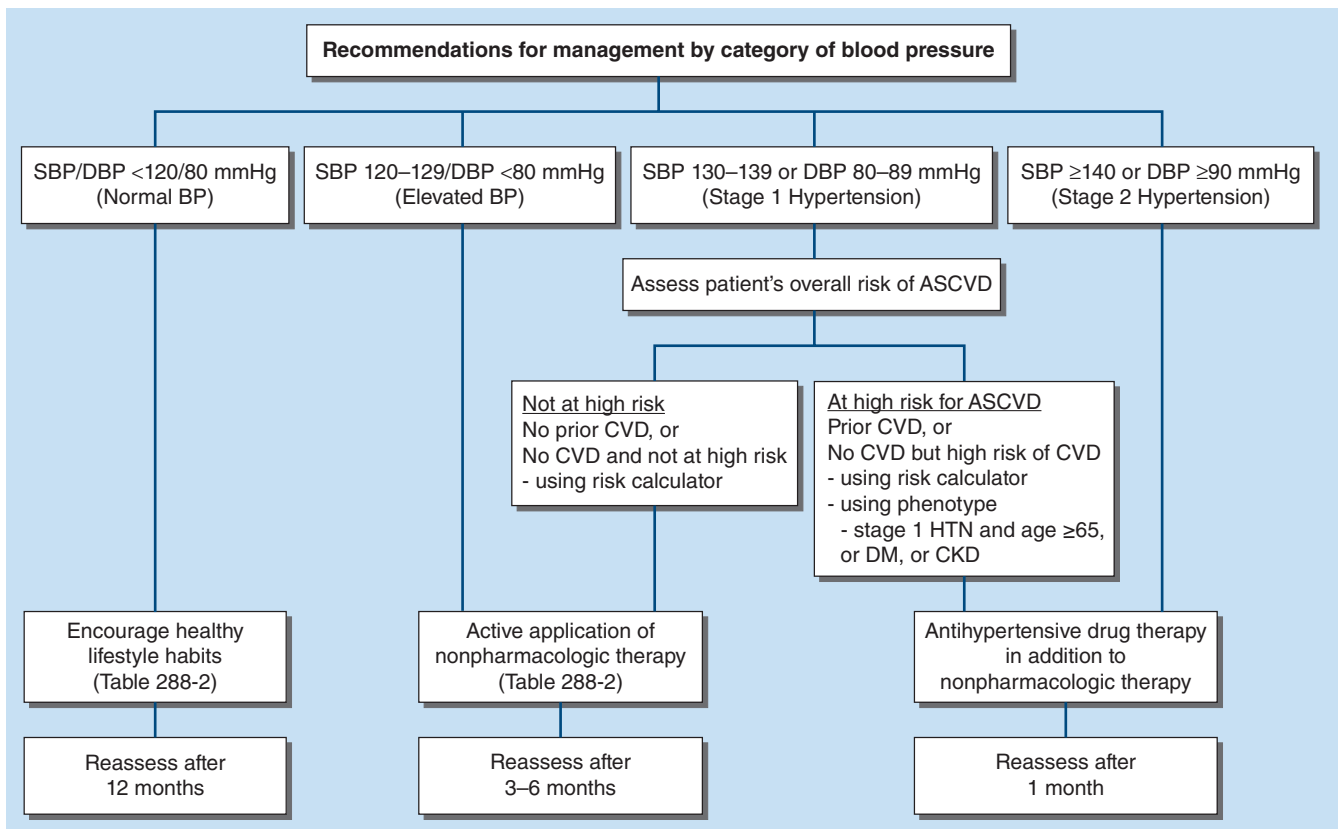


FIGURE 288-3 Recommendations for nonpharmacologic and antihypertensive drug therapy by category of blood pressure. ASCVD, atherosclerotic CVD; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic BP; DM, diabetes mellitus; HTN, hypertension; SBP, systolic BP.

been a consistent finding in trials that have evaluated the Mediterranean diet, low-carbohydrate diets, and vegetarian and vegan diets. The DASH (Dietary Approaches to Stop Hypertension) diet is a heart-healthy diet that was specifically formulated to lower BP. The DASH diet is high in vegetables, fruits, whole grains, and low-fat dairy products and low in fats, saturated fats, and cholesterol. It has been extensively evaluated, and many DASH resources and support systems are readily available to health care providers and the public. For these reasons, it is commonly recommended as the best heart-healthy diet choice for BP reduction. Many of the DASH evaluation trials have been conducted as feeding studies in which patients are given specially prepared foods as a replacement for their usual diet. Compared to trials based on behavior change, feeding studies require less effort by the patient, achieve greater intervention change, and generally report a greater reduction in BP. However, the results of feeding trials are less generalizable to clinical practice where provision of patient meals is infeasible. The DASH trials that have employed a behavior change strategy provide a better indication of what can be expected in clinical practice settings. In the original short-term (8-week) feeding trial, the DASH diet reduced SBP/DBP by 5.5/3.0 mmHg compared with the usual U.S. diet. In longer-term (6-month) behavior change trials, the DASH diet combined with other established nonpharmacologic recommendations for BP lowering reduced SBP and DBP by ~4 mmHg and 3 mmHg, respectively, compared to an advice-only intervention, and by 0.6 mmHg and 0.9 mmHg, respectively, compared to other established recommendations on their own. With good adherence, one could reasonably expect use of the DASH diet on its own to result in an average SBP reduction of ~5 mmHg in patients with and 2–3 mmHg in patients without hypertension. Community-based trials have demonstrated that the DASH diet components can be purchased at supermarket locations without the need for patients to pay for higher priced specialty food products. The DASH diet can be combined with other nonpharmacologic interventions such as weight loss, sodium reduction, or increased physical activity. Likewise, the DASH diet eating plan can be customized to meet an individual's other dietary requirements, meal preferences, and lifestyle.

Weight Loss Weight loss not only lowers BP but can also improve lipid levels and is effective for prevention and management of diabetes mellitus. It can be achieved through a combination of calorie reduction and increased physical activity. The most sustainable approach to weight loss is targeting gradual and progressive loss in weight. As with all behavior change strategies, weight loss can be difficult to achieve and even more difficult to maintain over long periods of follow-up. However, it can be successful, especially in motivated patients who receive high-quality counseling and clinician reinforcement. In addition to clinic-based interventions, many commercial and noncommercial providers offer weight loss programs. The commercial programs usually provide some or all of the recommended meals. The optimal goal is achievement of an ideal body weight, but any weight reduction is beneficial. Application of high-quality weight loss counseling usually results in 6- to 12-month weight loss of ~10 lb (4.5 kg). Typically, a 1-mmHg reduction in SBP can be expected for about every kilogram of weight loss. This translates to a 6- to 12-month average reduction in SBP of ~5 mmHg. The average reduction varies depending on the success of the intervention and the starting level of BP, with SBP reductions in those with and without hypertension tending to be about 5 and 2–3 mmHg, respectively. Several medications can be used to assist in weight loss, but some of the most popular agents, like sodium-glucose cotransporter 2 (SGLT2) inhibitors, are off-label options and are best reserved for U.S. Food and Drug Administration (FDA)-approved indications. Injectable glucagon-like peptide 1 (GLP-1) receptor agonists are equivalent agents that have been approved for weight loss by the FDA and have been shown to reduce weight in clinical trials. Certain patients with hypertension and a body mass index ≥ 35 kg/m² may be candidates for bariatric surgery. Selection of candidates for bariatric surgery is best conducted by multidisciplinary teams with experience in managing morbid obesity.

Dietary Sodium Reduction Many RCTs have demonstrated reductions in BP following decreases in dietary sodium intake. In a large dose-response meta-analysis of RCTs, there was a striking almost linear relationship between reduction in dietary sodium intake and

the corresponding decreases in BP. This finding was quite robust, being noted for every subgroup studied. An SBP/DBP difference of ~15/10 mmHg was noted between those with the highest (~7000 mg/d) and lowest (<1000 mg/d) intakes of sodium. An average reduction of ~5.5 mmHg was noted for every 2300-mg (100-mmol) decrement in dietary sodium intake. As expected, the effect was greater in adults with compared to those without hypertension and in SBP compared with DBP. The results were consistent with a “lower is better than higher” conclusion for intake of dietary sodium. In healthy U.S. adults, consumption of a diet with 1500 mg sodium provides adequate opportunity to meet the other recommended dietary requirements. Recommendations for daily sodium intake in adults vary considerably. The U.S. federal *Dietary Guidelines for Americans* recommends a daily sodium intake <2300 mg, whereas the World Health Organization recommends <2000 mg and others recommend much lower intakes. More than 95% of U.S. adults exceed the 2000 mg/d threshold, and almost 100% exceed the 1500 mg/d threshold. However, any reduction in dietary sodium intake is likely to be beneficial.

The traditional approach to reducing dietary sodium intake in clinical settings is by means of behavior change interventions. In addition to helping patients estimate and track their sodium intake, trying to avoid high-sodium foods and maximizing home preparations using fresh, natural foods are desirable. In countries like the United States, where most of the population consume commercial food products, >80% of an individual's sodium intake is generally due to sodium added during food processing or commercial preparation of foods and only ~10% is due to naturally occurring sources of sodium. Careful scrutiny of food labels for packaged foods while shopping, reducing meal portion size, choosing condiments and seasonings with low sodium content, salt substitution using herbs and spices, and use of salt substitutes that replace ~25% of the sodium content with potassium are other well-proven strategies to reduce dietary sodium intake. Salt substitutes provide a relatively easy and well-accepted way to achieve a modest reduction in sodium intake and an increase in potassium intake, especially in those who primarily eat foods prepared in the home and/or add a lot of salt at the table. A large cluster-designed clinical trial conducted in Chinese adults with stroke or at high risk for stroke demonstrated an impressive and statistically significant 14% reduction in stroke (the primary outcome), other major CVD events, and all-cause mortality in adults randomized to use a salt with 25% substitution of potassium for sodium compared to those who used regular salt. There was no evidence of a difference in hyperkalemic events in the two treatment groups. Public health messaging based on simple educational and action recommendations is also useful. Policy aimed at reducing the amount of sodium added to foods has great potential but has been difficult to implement in the United States. Long-term follow-up for 10–15 years in participants who had been randomized to a behavioral change sodium reduction intervention or usual care has also suggested a significant reduction of 30% in new-onset CVD events.

Potassium Supplementation A higher intake of potassium is associated with a lower BP and a reduced risk of CVD, especially stroke. U.S. Dietary Reference Intake committees have not made a dietary allowance intake recommendation due to insufficient evidence but have identified 2600 and 3400 mg/d in women and men, respectively, as adequate intake levels. Individual RCTs and meta-analyses provide strong evidence that potassium supplementation reduces BP. This has been achieved with pill therapy and dietary supplementation, with the latter being the preferred approach in clinical practice because this usually results in consumption of a more heart-healthy diet and a lower intake of dietary sodium. In most RCTs, routine potassium intake has been supplemented by about 2300 mg (60 mmol) per day, and the average reduction in SBP has been ~5 mmHg in trials with a successful intervention (net change in urinary potassium ≥20 mmol [870 mg] per day). As expected, the SBP reduction is greater in adults with (~5 mmHg) than without hypertension (~2 mmHg) trials. The SBP lowering is almost three times greater in black compared with white adults. Finally, there is a strong linear association between BP reduction with potassium supplementation and consumption of

dietary sodium, possibly reflecting the well-known natriuretic effects of potassium. A dose-response meta-analysis has suggested a U-shaped BP response to potassium intake, with an optimal supplemental intake of ~1200 mg/d. However, the unexpected BP response findings at the upper and lower end of the U-shaped curve were based on indirect estimates and a relatively small number of trials.

Many foods contain potassium, but fruits, vegetables, legumes, and leafy greens are especially high in potassium content. By design, the DASH diet targets provision of 4700 mg of potassium per day, exceeding the recommended intake of 3500 mg/d in U.S. adults. Potassium supplementation is contraindicated in patients with hyperkalemia or advanced kidney disease and in those taking pills that can block the urinary excretion of potassium, including potassium-sparing diuretics, inhibitors of the RAAS, and MRA agents, such as aldosterone, eplerenone, and finerenone.

Physical Activity Observational studies identify a strong inverse association between physical activity (leisure time or total) and BP as well as CVD. In like manner, high-quality RCTs have demonstrated that increased physical activity lowers BP in adults with and without hypertension. Most of the trials have been based on aerobic exercise interventions such as brisk walking, swimming, or dancing. Meta-analyses of aerobic exercise RCTs have been consistent in documenting substantial BP-lowering efficacy, but the quantitative estimates for average reduction in BP have varied considerably, with reports of 5–10 mmHg for SBP in studies restricted to adults with hypertension and 3–5 mmHg for studies in those without hypertension. Dynamic resistance exercises such as climbing stairs, push-ups, weightlifting, and squats have also been shown to lower BP and are often employed concurrently with aerobic exercise. Isometric resistance exercises, during which muscles or muscle groups are tightened without any visible movement of the surrounding joints, include yoga poses, wall sit, plank, and bench press exercises. Fewer high-quality RCTs have assessed the efficacy of isometric resistance exercise, but individual trials and meta-analyses indicate this approach is effective for BP lowering. In the largest meta-analysis (~400 trials) of physical activity, aerobic exercise reduced SBP by ~5 mmHg in adults with hypertension and when combined with dynamic resistance exercise by ~6.5 mmHg. In trials that allowed for a direct comparison with antihypertensive drug therapy, physical activity yielded an almost identical level of BP lowering. Most guidelines recommend moderate-intensity aerobic exercise as the principal approach to lowering BP but acknowledge that dynamic and isometric resistance exercises are a useful complement. Based on clinical trial evidence, an aerobic exercise duration of 40–60 min three or more times per week for a total ≥150 min per week may be optimal. Although more intensive physical activity may be ideal for overall cardiac fitness, less intensive physical activity is sufficient for BP reduction. Less frequent but more intensive physical activity (e.g., “weekend warrior” exercise) has been shown to lower BP.

Alcohol Consumption Alcohol has long been known to be a pressor. Observational dose-response meta-analyses demonstrate a roughly linear association between alcohol consumption and both BP and hypertension, with no threshold for the association. For each 14-mg increased intake of alcohol (amount in a U.S. standard alcoholic drink), SBP is ~1.5 mmHg higher. RCTs have studied the efficacy of reducing alcohol intake on BP by substitution of lower-alcohol or no-alcohol drinks, use of behavior change interventions, or abstinence without access to alcohol. The overall effect of alcohol reduction on SBP in the largest meta-analysis was a reduction of ~5.5 mmHg. However, the magnitude of the effect is greatly influenced by baseline level of BP and alcohol intake and by the success of the intervention. Most current U.S. guidelines recommend an alcohol intake goal of ≤2 and ≤1 standard drinks per day for men and women, respectively. In part, this reflects the possibility that a modest intake of alcohol may favorably influence other CVD risk factors, such as high-density lipoprotein cholesterol. The WHO recommends abstinence from alcohol.

Summary for Nonpharmacologic Interventions to Lower BP In summary, a strong body of evidence supports the value of

interventions based on the six exposures highlighted in Table 288-2. In general, the interventions exhibit a linear-type dose-response for BP reduction. Consequently, more successful interventions result in greater BP reduction, and even smaller than desired changes in the exposure are likely to be beneficial. In addition, greater BP lowering can be expected in adults with compared to adults without hypertension, in those who start with more abnormality in the exposure, and when two or more interventions are combined. For example, a greater reduction in BP can be expected when the intervention combines the DASH diet with weight loss or sodium reduction. However, the behavioral changes needed for combination interventions are typically more challenging and require a greater commitment by the therapist and patient. Finally, nonpharmacologic interventions often enhance the effect of antihypertensive medications. This has been especially well demonstrated for reductions in sodium intake. A practical approach is to focus initially on the behavior that is most abnormal and most amenable to change, with a longer-term goal of more comprehensive improvements. With the exception of salt substitution, change in BP has been the primary outcome in most of the nonpharmacologic treatment trials, but some have demonstrated improvements in intermediate CVD outcomes, especially left ventricular mass and left ventricular hypertrophy. In addition, randomized comparisons following long periods of posttrial follow-up have suggested CVD benefits for both sodium reduction and weight loss.

■ PHARMACOLOGIC THERAPY TO PREVENT CARDIOVASCULAR DISEASE

Efficacy of Pharmacologic Therapy in Uncomplicated Primary Hypertension In most adults, primary hypertension is uncomplicated and relatively easy to manage. The introduction of diuretics in the late 1950s and early 1960s revolutionized pharmacotherapy of high BP, and these drugs were the principal agents in the early antihypertensive drug treatment trials. The first antihypertensive drug RCT reported a substantial benefit of active therapy compared to placebo in 1966, but it was quickly superseded by two larger placebo-controlled multicenter Veterans Administration Cooperative Group RCT analyses. The first analysis was for adults with an average DBP between 115 and 129 mmHg, and this component was stopped early due to benefit and published in 1967. The second analysis, for adults with an average DBP between 90 and 114 mmHg, was published in 1970. Both analyses demonstrated that antihypertensive drug therapy resulted in a dramatic CVD benefit compared to placebo. Subsequent trials confirmed these findings and documented benefits when SBP reductions were targeted, either in combination with an elevated DBP or as an isolated elevation of SBP in older adults. In a group meta-analysis of 123 trials, active treatment resulted in a reduction of major CVD (20%), CHD (17%), stroke (27%), HF (28%), and all-cause mortality (13%). In this and other meta-analyses, the relative reduction in risk has been almost identical for those with or without prior CVD, albeit only adults at high risk for CVD could participate in the included trials, and benefit has accrued to those with a baseline SBP from 130 to 139 mmHg and above.

Choice of Antihypertensive Drug Classes Characteristics of the 11 most commonly used classes of antihypertensive medication, including examples, usual daily dosage, frequency of administration, proposed mechanism of action, approximate BP lowering compared to placebo, most common side effects, frequency of adverse events, and special aspects of the drug class are shown in Table 288-4.

Initial therapy with agents from five classes of drug therapy (diuretics, beta blockers, CCB, ACEI, and ARB) has been shown to prevent CVD compared to placebo. However, in head-to-head RCTs, beta blockers have been inferior to agents from the other four antihypertensive drug classes, especially for prevention of stroke. CCBs are good for prevention of stroke but inferior for prevention of HF, especially compared to diuretics. Generally, meta-analyses have identified diuretics as being the “best in class” for first-step prevention of CVD. Recognizing these differences in antihypertensive drug classes, RCTs and meta-analyses also provide evidence that BP lowering, however achieved, is more

important than the drugs used to achieve it. Most clinical practice guidelines, including the U.S. ACC/AHA BP guideline, recommend an approach similar to that outlined in Fig. 288-4 in which diuretics, CCBs, and ACEIs or ARBs, alone or in combination, are used for initial drug therapy in patients without a compelling indication for use of a beta blocker.

One or more nonpharmacologic therapies should be used to manage adults with stage 1 hypertension who are not at high risk for CVD (no CVD and a calculated 10-year risk of ASCVD <10% based on use of the ACC/AHA pooled cohort equations calculator). If BP cannot be controlled to an SBP/DBP <130/80 mmHg after 6 months of nonpharmacologic therapy, it may be reasonable to add an antihypertensive medication, especially in younger adults with a high lifetime risk of ASCVD. The latter can be estimated using a calculator that is readily available on the ACC website and elsewhere. Antihypertensive drug therapy should be used in addition to nonpharmacologic therapy in adults with stage 1 hypertension who are at high risk for ASCVD and for all individuals with stage 2 hypertension. A minority of such persons with an average SBP/DBP close to 130/80 mmHg can be managed successfully with single antihypertensive agent combined with nonpharmacologic therapy. However, most patients with hypertension require treatment with more than one antihypertensive agent. This is especially the case for adults with stage 2 hypertension with an SBP ≥140 mmHg and all non-Hispanic black adults with hypertension.

In clinical practice settings, it is common for patients with hypertension to have other comorbid conditions, including diabetes mellitus, CHD, and CKD, requiring use of agents from other drug classes that concurrently lower BP. Longer-acting versions of the recommended four first-step drug classes should be used to ensure the adequacy of once-daily treatment. For example, longer-acting diuretics such as chlorthalidone or indapamide are preferred over shorter acting agents such as hydrochlorothiazide because the long half-life of these agents is better suited for the provision of nighttime as well as daytime control of BP and because chlorthalidone has been used in almost all of the landmark U.S. trials of antihypertensive drug treatment. The most common side effects with thiazide and thiazide-like diuretics are biochemical changes, such as hypokalemia and slight increases in blood glucose. Potassium-sparing agents, such as amiloride or triamterene, can be combined with diuretics to counter these effects. The biochemical changes with diuretics are generally mild and do not counteract their well-proven CVD benefits. Although there are differences between individual ACEI agents, their clinical effects are more similar than different. Use of longer-acting agents such as lisinopril is preferred. The most common problematic side effect with ACEIs is a dry cough. This side effect is usually resolved quickly by switching to a corresponding dosage of an ARB. Side effects with ARBs are rare. ACEIs and ARBs should not be used in combination because this unnecessarily increases the risk of hyperkalemia, especially in vulnerable patients and provides little if any additional benefit over using either drug class on its own. Neither an ACEI nor an ARB should be used in pregnancy or planned pregnancy due to the risk of teratogenic side effects in the fetus. In contrast to the other antihypertensive drug classes, there are substantial clinical differences between dihydropyridine and nondihydropyridine CCB agents, with the former being primarily vasoactive and the latter having greater effect on the heart. Typically, dihydropyridine CCBs should be used in the treatment of hypertension. Peripheral edema occurs in ~10% of patients taking dihydropyridine CCBs but is often mild and can be minimized by dose reduction or eliminated by switching to an agent from another class. Nondihydropyridine CCBs should rarely be employed to treat hypertension unless there is another compelling indication for their use. Particular caution is necessary in patients at risk for bradycardia, heart block, or HF.

The earliest beta blocker drugs were relatively nonselective blockers of β -adrenergic receptors, including the heart (β_1 receptors) and lungs (β_2 receptors). They are rarely prescribed for hypertension due to the potential for bronchospasm. The second class of beta blocker agents, including metoprolol, contain more cardioselective and longer-acting drugs. Although cardioselective, atenolol is not recommended because several meta-analyses have reported that it has been less

TABLE 288-4 Summary Information for the Major Antihypertensive Drug Classes Used to Manage High Blood Pressure

CLASS	EXAMPLES	DOSE RANGE, mg	DOSE FREQUENCY/D	METHOD OF ACTION	SBP REDUCTION VERSUS PLACEBO, mmHg (APPROXIMATE)	MOST COMMON ADVERSE EFFECTS	FREQUENCY OF ADVERSE EVENTS	COMMENTS
First-Step Drugs								
Diuretics (thiazide and thiazide-like).	Chlorthalidone Hydrochlorothiazide Indapamide	12.5–25 12.5–50 1.25–2.5	1 1 1	Block sodium reabsorption in distal convoluted tubule	12	Hyponatremia Hypokalemia Hypercalcemia Hyperuricemia Hyperglycemia Dyslipidemia	Similar to placebo	Chlorthalidone preferred due to long half-life and use in most U.S. trials
ACE inhibitors	Enalapril Lisinopril Benazepril Ramipril Trandolapril	5–40 10–40 10–40 2.5–20 1–4	1 or 2 1 1 or 2 1 1	Inhibit ACE activity and Ang II production	12.0	Cough Hyperkalemia in CKD AKF in severe bilateral RAS Hypotension Angioedema	Similar to placebo	Do not use in combination with ARB; contraindicated in pregnancy
ARB	Losartan Valsartan Azilsartan Candesartan Olmesartan	50–100 80–320 40–80 8–32 20–40	1 or 2 1 1 1 1	Block Ang II binding to Ang receptors	12	Hyperkalemia in CKD Reduced GFR AKF in severe bilateral RAS Hypotension	Similar to placebo	Do not use in combination with ACE inhibitor; contraindicated in pregnancy
CCB (DHP)	Amlodipine Felodipine Nifedipine LA	2.5–10 2.5–10 30–90	1 1 1	Blocks calcium from entering cells, primarily inhibiting vasoconstriction	10	Peripheral edema (dose-dependent) Gingival hyperplasia	Similar to placebo	Amlodipine may be preferred CCB if tolerated Not recommended in HFrEF
CCB (non-DHP)	Diltiazem ER Verapamil ER	120–360 100–300	1 1 (evening administration recommended)	Blocks calcium from entering cells, reducing heart rate and vasoconstriction	9.0	Bradycardia Nausea Constipation.	Similar to placebo	Do not use in combination with β -blockers Do not use in HFrEF or in high-grade AV or SA block
Other Drugs								
β -Blocker	Metoprolol Carvedilol Nebivolol	50–200 20–80 5–40	1 1 1	Block β -adrenergic receptors	10	Asthma Bradycardia Fatigue Exercise intolerance Impaired concentration	Similar to placebo	First-step drugs when clinically indicated, e.g., in IHD and HF Contraindicated in high-grade heart block
MRA	Spironolactone Eplerenone Finerenone	25–100 50–100 10–20	1 2 1	Block distal tubule mineralocorticoid receptor activity	9	Hyperkalemia, especially in CKD and with potassium-sparing agents Spironolactone may cause tender breasts, gynecomastia, and erectile dysfunction in men	9–20%	Especially useful in resistant hypertension and low-renin states
K ⁺ -sparing diuretics	Amiloride Triamterene	5–10 50–100	1 or 2 1 or 2	Block distal tubule sodium reabsorption	NA	Hyperkalemia, especially in CKD or with other agents that favor potassium retention	Similar to placebo	Minimal effect on BP Used to counteract hypokalemic effect of diuretics

(Continued)

TABLE 288-4 Summary Information for the Major Antihypertensive Drug Classes Used to Manage High Blood Pressure (Continued)

CLASS	EXAMPLES	DOSE RANGE, mg	DOSE FREQUENCY/D	METHOD OF ACTION	SBP REDUCTION VERSUS PLACEBO, mmHg (APPROXIMATE)	MOST COMMON ADVERSE EFFECTS	FREQUENCY OF ADVERSE EVENTS	COMMENTS
Loop diuretics	Furosemide Torsemide	20–80 5–10	2 1	Inhibits reabsorption of sodium in loop of Henle	NA	Hypokalemia Volume depletion Hyperuricemia	Infrequent	Preferred in CKD with GFR <30, in symptomatic HF, and when using potent direct vasodilator minoxidil
α_1 -Receptor blockers	Doxazosin	1–16	1	Inhibit α_1 -adrenergic receptors	5	Orthostatic hypotension, especially in older adults	9%	Less cardioprotective than diuretics Mostly used in men with prostrate hypertrophy
Direct vasodilator	Hydralazine Minoxidil	100–200 5–100	2 or 3 1–3	Dilate peripheral arterioles	NA	Reflex tachycardia Fluid retention Hydralazine-induced lupus syndrome (rare) Minoxidil-induced hirsutism in women	Up to 80%	Potent antihypertensive agents Usually reserved for fourth- or fifth-step treatment in resistant hypertension Usually combined with diuretic (loop agents for minoxidil) and β -blocker to minimize side effects
Central α_2 -agonist and other centrally acting drugs	Clonidine (oral) Clonidine patch Guanfacine Methyldopa	0.1–0.8 0.1–0.3 0.5–2.0 250–1000	2 1/wk 1 2–3	Stimulate central nervous system α_2 -adrenergic receptors	NA	Sedation Dry mouth Bradycardia Fatigue Constipation Orthostatic hypotension.	6–20%	Infrequently used due to side effects and potential for hypertensive crisis following abrupt withdrawal Methyldopa has a good safety record in pregnancy

Note: Adverse event estimates based on U.S. Food and Drug Administration labeling at <http://dailymed.nlm.nih.gov/dailymed/index.cfm>. Estimates of BP lowering versus placebo are “artificially” higher with older agents than with newer agents because the former were compared to placebo alone, whereas the latter were evaluated in patients who were already being treated with other antihypertensive medications.

Abbreviations: ACE, angiotensin-converting enzyme; AKF, acute kidney failure; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; DHP, dihydropyridine; ER, extended release; GFR, glomerular filtration; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; LA, long acting; MRA, mineralocorticoid receptor antagonist; NA, not applicable; RAS, renal artery stenosis; SA, sinoatrial.

cardioprotective than other drug classes, including diuretics, when used for treatment of hypertension. The third-generation beta blocker drugs are cardioselective and have additional vasodilatory properties (nebivolol), used alone or in combination with α -receptor blockade (carvedilol). No RCT has documented improved CVD event protection with use of the newer agents. The remaining agents in Table 288-4 are covered in other sections of this chapter.

It has become increasingly clear that starting with lower doses of a two-drug combination provides superior BP control and results in fewer side effects compared to use of a single drug at a high dose. Initial therapy is especially important because surveys of clinical practice have repeatedly demonstrated that the initial drug choice is often materially unaltered due to therapeutic inertia despite unsatisfactory BP control. RCTs using stepped-care drug therapy, in which antihypertensive medications are added sequentially if BP control has not been achieved at full doses of the proceeding drugs, demonstrate that this approach can be successful if well applied. However, initial combination drug therapy has proven to be more effective for rapid achievement of target BP and medication adherence compared to the stepped-care approach.

Antihypertensive drug combinations should be based on use of drugs with complementary physiologic actions. For example, a diuretic or CCB combined with an ACEI or ARB is suitable for dual therapy and a diuretic combined with a CCB and an ACEI or ARB for triple-therapy combinations. Use of single-pill combinations results in better adherence compared to treatment with multiple drugs. In RCTs, the average number of drugs to achieve an SBP/DBP <140/90 mmHg has been two and to achieve an SBP/DBP <130/80 mmHg has been three.

Antihypertensive Treatment Blood Pressure Target Many clinical trials have reported better prevention of CVD in groups randomized to lower compared with higher achieved treatment BPs. Meta-analyses of RCTs to compare different achieved BPs have typically pooled the experience in trials that compared active versus placebo treatments, more versus less intensive treatments, and groups randomized to different BP targets. Most of these meta-analyses have reported greater benefit for a lower versus higher achieved BP, with the benefit being greatest for those who start at a higher BP and achieve a greater reduction in BP than their counterparts who achieve the

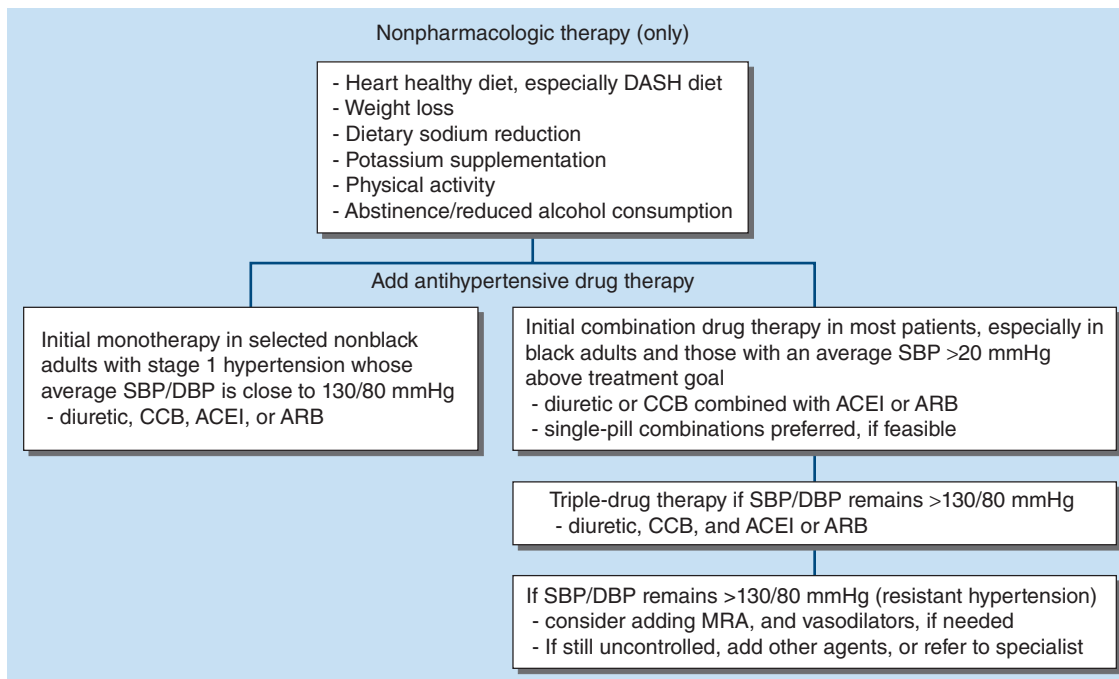


FIGURE 288-4 Overview of specific antihypertensive treatments in adults with uncomplicated hypertension. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic BP; MRA, mineralocorticoid receptor antagonists; SBP, systolic BP.

same BP but start from a lower level of BP. As one would expect from the observational association between BP and CVD, the incremental benefit for CVD protection diminishes as the category of achieved BP gets progressively lower. Almost all of the meta-analyses, including one conducted for the ACC/AHA BP clinical practice guideline committee, have reported that an achieved SBP of <130 mmHg is superior to higher categories of achieved SBP. The major English-language clinical practice guidelines recommend SBP treatment targets that vary from 120 to 135 mmHg in adults with hypertension and a high risk of ASCVD. Surveys indicate that almost all patients with hypertension who are seen in clinical practice are at high risk for ASCVD. At the current time, an SBP/DBP treatment goal of 130/80 mmHg in adults with hypertension, as recommended in the ACC/AHA BP guideline, seems reasonable. The only exception is in noninstitutionalized community-dwelling older adults, arbitrarily defined as ≥ 65 years, where the goal should be to achieve an SBP <130 mmHg. For older adults with hypertension and a high burden of comorbidity who have a limited life expectancy, clinical judgment and patient preference should form the basis for decisions regarding the potential value and intensity of BP treatment. An SBP/DBP treatment goal of <130/80 mmHg should not preclude the possibility of achieving a greater reduction in BP in those who tolerate their BP-lowering treatment without evidence of adverse effects. In all four of the RCTs that have compared randomization to an SBP goal of 120 versus 140 mmHg, fewer CVD complications have been noted in the group assigned to the lower BP, albeit this has only been statistically significant in two of the four trials. Three additional large 120 versus 140 mmHg RCTs are expected to report in the near future, which should result in more definitive guidance for a 120 versus 130 mmHg SBP target.

Resistant Hypertension Failure to control SBP/DBP to <130/80 mmHg with three antihypertensive medications, preferably including a diuretic, or taking four or more antihypertensive medications to achieve an SBP/DBP <130/80 mmHg is designated as apparent resistant hypertension. A general approach to the investigation and management of apparent resistant hypertension is outlined in [Fig. 288-5](#).

First, pseudo-resistance due to inaccurate BP measurement should be excluded. Next, accurately measured out-of-office BP readings should be obtained to exclude white coat hypertension. After this important issue is addressed, lifestyle, OSA, use of medications that

raise BP, and other secondary causes of hypertension should be excluded. Management of resistant hypertension starts with confirmation of adherence to the prescribed treatment regimen because lack of adherence to lifestyle change advice and medication nonadherence are common explanations for apparent resistant hypertension. It is also important to ensure that the medication regimen is based on use of long-acting, once-daily agents. This is especially true for diuretics, where shorter acting agents such as hydrochlorothiazide should be replaced by chlorthalidone or indapamide. If the antihypertensive medications have been prescribed as separate pills, conversion to a single pill combination is highly desirable. After this issue is addressed, an MRA such as spironolactone should be added to the regimen ([Table 288-4](#)). Most patients tolerate spironolactone, but in a minority, laboratory abnormalities such as hyperkalemia or side effects such as dizziness, leg cramps, and gynecomastia can be troublesome, especially in men. Many of the spironolactone side effects can be avoided by use of newer but more expensive MRA agents such as eplerenone and, especially, the nonsteroidal finerenone. In 2023, the U.S. FDA approved the use of ultrasound and radiofrequency renal denervation therapy as adjunctive treatments in patients with resistant hypertension. Consideration of renal nerve denervation (RDN) should be restricted to patients with true resistant hypertension and an office SBP ≥ 160 mmHg.

Treatment of Hypertension in Special Groups Certain patient groups have characteristics that warrant special attention. The following are some of the more important groups.

PATIENTS WITH CVD The combination of hypertension and CVD is very common. Choice of antihypertensive agents is commonly influenced by the specific type of CVD, but use of ACEI, ARB, or beta blockers is common, often accompanied by diuretics, CCB, and MRA. Additional treatment with SGLT2 inhibitors may be indicated, especially in those with HF and diabetes mellitus. Nondihydropyridines should be used with caution in patients with bradycardia or the potential for heart block. In general, the standard treatment goal of SBP/DBP <130/80 mmHg is indicated if well tolerated.

KIDNEY DISEASE Hypertension is very common in patients with CKD, becoming more prevalent with increasing severity of CKD, such that 80–85% of those with advanced kidney disease have concurrent hypertension. High BP is a risk factor for CKD and ESKD, but the interaction between BP and kidney disease is complex, making it difficult

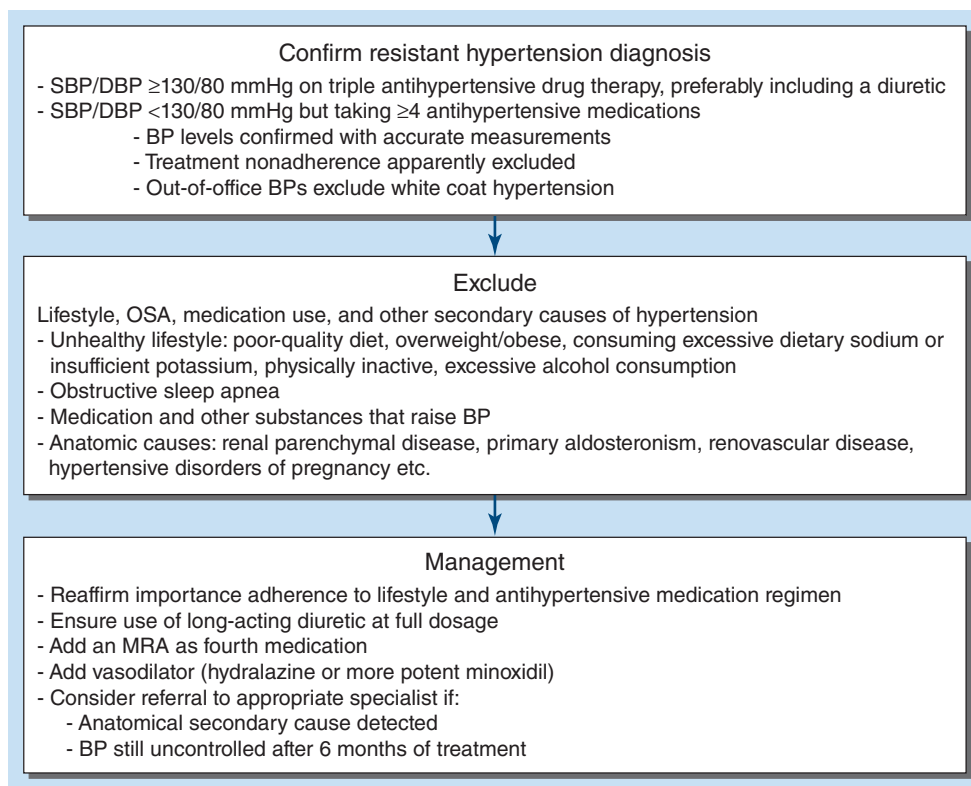


FIGURE 288-5 Confirmation and management of resistant hypertension. BP, blood pressure; DBP, diastolic blood pressure; MRA, mineralocorticoid receptor antagonist; OSA, obstructive sleep apnea; SBP, systolic blood pressure.

to determine cause and effect. Patients with kidney disease have a high prevalence of both traditional and novel risk factors for CVD, including markers of inflammation and endothelial dysfunction. As a result, the burden of CVD complications is high in adults with kidney disease, and patients with ESKD are more likely to die from CVD than from other complications of kidney failure. Managing hypertension in adults with advanced kidney disease can be difficult because they frequently have a combination of increased vascular resistance and intravascular volume overload and can exhibit vascular instability with wide swings in BP that complicates management. Normally, preglomerular vasoconstriction decreases the pressure to which the glomerulus is exposed and optimizes filtration without damaging the glomerulus. The efferent glomerular arteriole can play a supplementary role, as needed, to regulate intraglomerular pressure. When kidney disease is present, the ability to regulate intraglomerular pressure is diminished, with the result that it rises and results in physical damage, a pathophysiologic process that often manifests in proteinuria and diminished glomerular filtration as the number of functioning nephrons declines.

Generally, patients with kidney disease and hypertension require several antihypertensive agents in addition to nonpharmacologic counseling, especially focused on sodium reduction. Antihypertensive drugs that block the RAAS such as ACEIs and ARBs play a central role because they can preserve glomerular function by inducing efferent arteriolar dilatation and reducing intraglomerular pressure. They are particularly important in patients with proteinuria and advanced kidney disease. Diuretics also play an important role because they can concurrently reduce peripheral resistance and intravascular volume. Traditionally, loop diuretics have been recommended in place of thiazide or thiazide-like diuretics in patients with an eGFR of ~ 30 mL/min per 1.73 m² or lower, but a recent high-quality RCT in patients with stage 4 kidney disease (average eGFR < 23 mL/min per 1.73 m²) demonstrated substantially lower (10.5 mmHg) reduction in ambulatory BP and a halving of urinary albumin/creatinine ratio in those randomized to chlorthalidone (12.5–50 mg) compared to placebo. Although CCBs tend to dilate the preglomerular afferent artery, they have a good safety record in kidney disease patients when used in combination with an ACEI or ARB. Single-pill antihypertensive combinations are especially

useful in patients with kidney disease because they are usually taking a large number of medications. Electrolyte levels should be monitored carefully, especially serum potassium levels, in kidney disease patients who are treated with potassium-sparing agents, including ACEI, ARB, and MRA drugs. Dual therapy with an ACEI, ARB, or ACEI-ARB combination is dangerous because of the risk of hyperkalemia and decline in kidney function.

PATIENTS WITH DIABETES MELLITUS The combination of hypertension and diabetes is common, resulting in a substantial risk for CVD and kidney disease. In patients with longstanding severe diabetes mellitus, autonomic neuropathy or volume depletion can cause orthostatic hypotension (10 mmHg difference in SBP between sitting and upright pressures), making management of hypertension difficult and requiring careful monitoring. Symptomatic hypotension (syncope) is a more important finding and may require a stepdown in antihypertensive therapy. Numerous RCTs in adults with diabetes have demonstrated that antihypertensive drug therapy reduces the risk of ASCVD, HF, and microvascular complications. The recommended antihypertensive treatment target is an SBP/DBP $< 130/90$ mmHg. Almost all patients with hypertension and diabetes mellitus require antihypertensive combination therapy, with many requiring three or four agents to achieve satisfactory BP control. Inclusion of an ACEI or ARB in the combination is recommended, especially in those with heavy proteinuria or kidney insufficiency. In addition, most patients require a diuretic. CCBs are commonly part of the antihypertensive drug regimen as well. In patients with diabetes mellitus and resistant hypertension, the addition of an MRA has been effective; however, serum potassium should be monitored carefully. Many drugs used to treat diabetes mellitus affect BP. Perhaps the best documented are SGLT2 inhibitors, which in meta-analyses result in an SBP/DBP reduction of $\sim 5/2$ mmHg, a modest reduction that does not meet the FDA requirement for classification as an antihypertensive agent. Given that patients with diabetes mellitus are often taking many medications, use of single-pill dual- or triple-combination therapy is especially useful.

OLDER ADULTS Vascular stiffening increases with aging, and as a result, isolated elevation of SBP and a wide pulse pressure are common

in older adults. Comorbidity is common, resulting in the potential for a compelling nonhypertensive indications for use of BP-lowering agents. Drug-drug interactions and delayed drug excretion due to kidney or liver disease are also possible. Despite these challenges, most older adults with hypertension can be treated in a manner similar to younger patients. Indeed, the RCT evidence for antihypertensive drug therapy generally comes from studies in which the average age was close to 70 years at baseline. Older adults tend to be at high risk for CVD and all-cause mortality and have a disproportionately large treatment-related reduction in the absolute CVD and all-cause mortality benefit. A natural concern in treating hypertension in older adults is the potential for excessive BP reduction resulting in syncope and resultant falls, or organ hypoperfusion with resultant infarction, especially in the distribution of the coronary arteries. Thus far, RCTs of antihypertensive drug treatment in older adults have been reassuring, resulting in substantial prevention of CVD and all-cause mortality with limited evidence of adverse events. An increased incidence of hypotension has been noted in some but not all trials of antihypertensive treatment in older adults. However, there has been no evidence of a resultant increase in syncope, falls, or infarctions in the RCTs. Nonrandomized analyses of data sets have identified a J-shaped association between BP and CVD risk. However, J-curves are common in observational epidemiology, and randomized comparisons, which are more helpful in guiding treatment decisions, have revealed prevention of CVD and all-cause mortality in those randomized to more versus less intensive antihypertensive therapy at any point in the J-curve. A reasonable approach is to initiate or enhance existing treatment using lower doses of medications than in younger patients. Because congestive heart failure becomes increasingly common at older age, use of a diuretic rather than a CCB for dual-therapy combinations with an ACEI or ARB is sensible. Many older patients require triple therapy or have comorbidities that necessitate treatment with a CCB. As is the case generally, BP lowering is more important than the treatment combination used to achieve the desired SBP goal of <130 mmHg. Recent trials have provided compelling evidence that more intensive antihypertensive treatment in older adults reduces the risk of cognitive impairment compared to less intensive treatment, and increasing evidence suggests that it reduces the risk of dementia.

RACE/ETHNICITY Non-Hispanic blacks have disproportionately high BP levels and higher prevalence of hypertension compared to whites and other major race/ethnicity groups in the United States. In addition, hypertension tends to occur earlier in life and is associated with a higher risk of CVD and kidney disease in blacks compared to whites and the other major race/ethnicity groups. Non-Hispanic blacks have the highest awareness of hypertension of any race/ethnicity group in the United States and have an antihypertensive drug treatment rate that is at least as high as that of whites. However, their rate of control to $<140/90$ mmHg in the 2017–2020 NHANES survey was 15% lower than in whites (37 vs 52%) and 6% lower for the $130/80$ mmHg cut point (20 vs 26%). Genetic differences seem to explain a small fraction of the high prevalence of hypertension in black Americans, but most of the disparity is likely due to differences in the social determinants of health, including access to and quality of education and health care, neighborhood of residence and the related built environment factors, economic instability, and the social and community context. The BP, CVD, and kidney disease health discrepancies between black and nonblack U.S. adults are not only sizable but have also been persistent, with little improvement in recent decades. RCT experience demonstrates that the gap can be eliminated with high-quality care, but following termination of RCT care, there has been a relatively rapid reversion to previous patterns of inadequate BP control. Resolution of the situation is unlikely without structural change in the approach to provision of care and a multilevel effort that involves patient engagement, a team-based approach to care that frees up clinicians to address social determinants of health, health system policies that enhance the provision of high-quality care, and payors with a focus on quality and use of contemporary BP goals for BP control. Diuretics and CCBs are especially effective for lowering BP in U.S. blacks, but many patients

require triple antihypertensive therapy, and use of BP-lowering agents for management of comorbid conditions is common.

SEX Although there are well-described differences in the underlying pathophysiology of hypertension in women and men, RCT experience indicates a similar benefit in prevention of CVD in both sexes in the landmark antihypertensive drug treatment trials. In the United States, women are more likely to be aware of hypertension, to be treated with antihypertensive medication, and to achieve the desired level of BP control compared with men, especially at younger ages. ACEIs and ARBs should not be used in pregnancy or women of child-bearing age who are contemplating pregnancy. Antihypertensive agents with a good safety record in pregnancy are highlighted in the section on hypertension in pregnancy. Observational studies and RCTs, including meta-analyses, have reported a reduced risk of fractures in women being treated with thiazide diuretics. This is postulated to result from decreased urinary calcium excretion and increased osteoblast cell formation. In contrast to thiazide diuretics, loop diuretics increase urinary calcium excretion. However, analyses of large observational studies have failed to associate loop diuretic use in postmenopausal women with fractures or a decrease in bone marrow density. Women report more cough with ACEIs and more pedal edema with CCB treatment compared with men.

Hypertensive Urgencies and Emergencies Adults presenting with a very high level of BP, usually designated as an SBP/DBP $\geq 180/100$ mmHg, should be classified as having a hypertensive urgency if they are asymptomatic or a hypertensive emergency if there is evidence of active ongoing hypertensive end-organ damage such as hypertensive encephalopathy, often manifesting with headaches, vision defects, nausea, vomiting, seizures, acute left ventricular failure, or acute kidney failure. Hypertensive urgency is far more common than hypertensive emergency and should be treated with institution, reinstitution, or intensification of oral antihypertensive agents in an outpatient setting. In contrast, a hypertensive emergency requires immediate, carefully supervised management with intravenous antihypertensive agents in an emergency room or inpatient setting. A hypertensive emergency associated with acute aortic dissection, eclampsia or severe preeclampsia, or a pheochromocytoma in crisis signals the need for particularly rapid care. Several drug classes can be used intravenously to achieve a rapid reduction in BP. Intravenous sodium nitroprusside is a potent vasodilator with a long history of success in managing hypertensive emergencies but must be monitored carefully to avoid overshooting the goal BP and causing hypotension. The dihydropyridine CCB nicardipine, given intravenously, is perhaps the most commonly utilized agent for acute BP reduction in patients with a hypertensive emergency in the contemporary practice of medicine. No dose adjustment is required for its use in older adults, but it is contraindicated in patients with severe aortic stenosis. Intravenous administration of the beta blocker labetalol is also effective but is contraindicated in patients with obstructive airways diseases, chronic obstructive pulmonary disease, bradycardia, or second- or third-degree heart block. Whichever drug is employed, a reduction rather than immediate normalization of BP is sufficient, with subsequent management of the patient's hypertension with oral agents. Secondary causes of hypertension, especially renovascular disease, are relatively common in patients with a hypertensive emergency and should be considered after the immediate reduction in BP.

PREVALENCE, AWARENESS, TREATMENT, AND CONTROL OF HYPERTENSION

NHANES provides a way to monitor prevalence, awareness, treatment, and control of hypertension in the U.S. general population. The NHANES definition of hypertension is based on BPs measured at a single visit, which results in an overestimation of hypertension, and the NHANES definition of treatment and control do not take into account nondrug therapy of hypertension. However, the methods used in NHANES have been consistent and careful over time, providing very helpful estimates for the temporal trends in hypertension prevalence and BP control. NHANES hypertension prevalence estimates have been fairly stable at ~46 and 32% for definitions based on use of the

SBP/DBP cut points of 130/80 and 140/90 mmHg, respectively, with higher prevalence rates in older versus younger adults, non-Hispanic blacks versus all other major race/ethnicity groups, and men compared with women. Treatment (with antihypertensive agents) and hypertension control rates increased progressively until about 2009–2012, with close to 53% of U.S. adults being controlled to an SBP/DBP <140/90 mmHg (the recommended goal at the time) and ~26% for an SBP/DBP <130/90 mmHg. After that, there was a progressive decline in control rates, with ~48 and 24% having an SBP/DBP <140/90 and <130/80 mmHg, respectively, by 2017–2020. The percentage controlled was higher when the analysis was confined to adults being treated for hypertension, but the temporal trends pattern was similar. The decrement in hypertension control was especially prominent in adults ≥ 75 years old. There has been a persistent gap in hypertension control rates between non-Hispanic black adults and all other race/ethnicity groups in the United States, with the percentage of non-Hispanic blacks and whites controlled to an SBP/DBP <140/90 mmHg in 2017–2020 being ~37 and 52%, respectively (20 and 26% for an SBP/DBP <130/80 mmHg). Worldwide, the situation is worse, with a recent global estimate reporting control to an SBP/DBP <140/90 mmHg in <14% of adults and in <8% of adults in low- and middle-income countries, where most of the world's population resides.

■ IMPROVING THE CONTROL OF HYPERTENSION

Clearly, the current hypertension control rates are unacceptable, and the traditional model of one-on-one physician-patient care for hypertension is not yielding a satisfactory outcome. Primary care physicians, who care for most patients with hypertension, are overburdened with responsibilities and have very limited time for direct provision of care in those with “routine” uncomplicated hypertension. A number of approaches have been shown to improve hypertension control rates in RCTs and clinical practice settings. Among these, team-based care has resulted in the biggest improvement in RCTs and meta-analyses. In the typical model of team-based care for hypertension management, a physician coordinates care provided by a team that may include nurses, pharmacists, community health care workers, social workers, lifestyle counselors, medical technicians, or others who have been specially trained in the provision of hypertension care. The specifics of the team composition depend on what is feasible in a practice setting and can be extended to engage front-office staff, spouses/partners, and close friends. In RCTs, team-based care has resulted in an average SBP reduction of ~7 mmHg, but in a recent high-quality, well-executed RCT, the SBP reduction exceeded 23 mmHg. It has been especially effective when trained nonphysician professionals have had the authority, usually with physician oversight, to prescribe antihypertensive medications in patients with uncomplicated hypertension. This frees up physician time to address patients with more complex care requirements. Most team-based care interventions have been multifaceted, incorporating health counseling, home BP monitoring (HBPM) and electronic support systems, and use of simple algorithms for health counseling and management of antihypertensive drug therapy. HBPM provides an excellent way to engage patients in their own care and to complement office BP management (OBPM) for monitoring long-term control of hypertension. Use of HBPM mandates advising patients on the purchase of clinically valid BP measurement devices and training in accurate measurement of BP (see BP measurement section). In U.S.

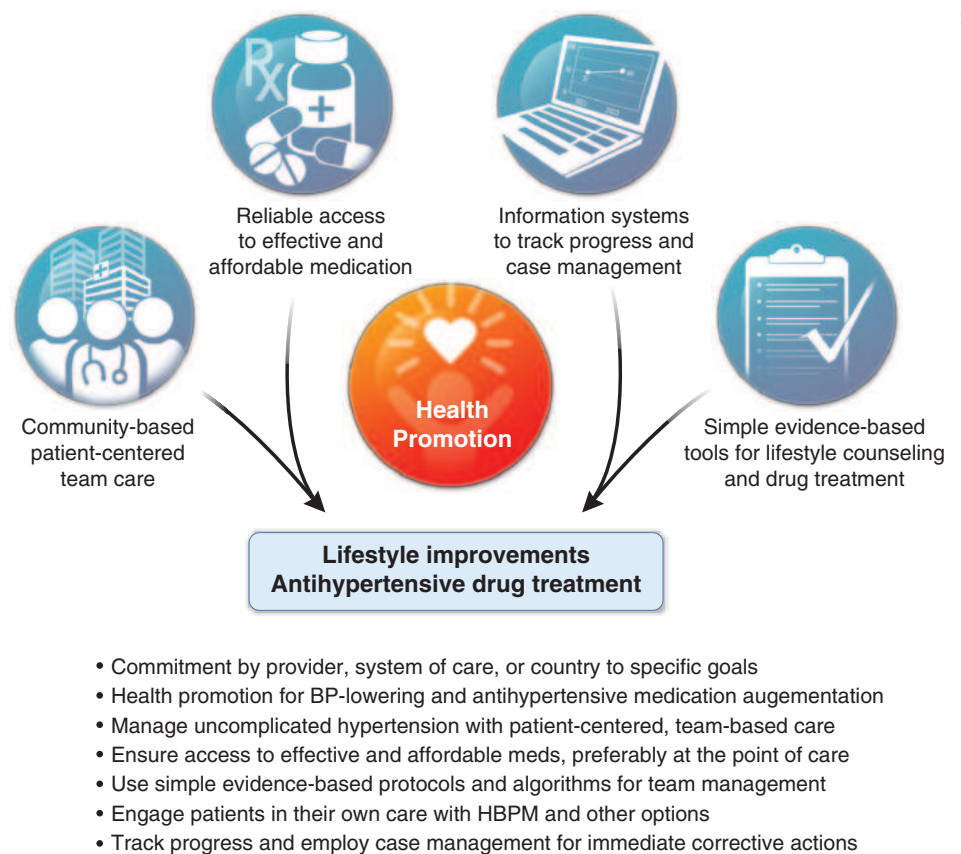


FIGURE 288-6 Best practices for control of hypertension. BP, blood pressure; HBPM, home blood pressure monitoring.

adults, getting three morning (prior to taking BP medications) and three evening HBPM measurements for 3 days prior to a clinic visit is a reasonable strategy for assessing average home BP. Team-based care approaches have not only been successful in RCTs but also yielded excellent results in clinical practice settings, with Kaiser-Permanente, Northern California reporting an improvement in SBP/DBP control to <140/90 mmHg from 44% in 2001 to 90% in 2015 based on institution of a multifaceted systemwide program of health care quality improvement that incorporated many of the previously mentioned approaches. Likewise, many of these approaches have been used to good effect in the U.S. Department of Veterans Affairs Health System. An overall best practices approach is outlined in [Fig. 288-6](#).

While it may not be possible for an individual practitioner to implement all of the suggestions in the figure, they should advocate for those that are beyond their direct control. There is great need to improve the management and control of hypertension in the United States and worldwide. Hypertension is among the most important, prevalent, modifiable, and cost-effective risk factors for CVD, kidney disease, and all-cause mortality. Its detection, treatment, and control should be a high priority for individual clinicians, systems of care, and countries worldwide.

■ FURTHER READING

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289 Renovascular Disease

Stephen C. Textor*



The renal vasculature is unusually complex with high arteriolar flow to the cortex in excess of metabolic requirements, consistent with its primary function as a filtering organ. After delivering blood to cortical glomeruli, the postglomerular circulation supplies deeper medullary segments that support energy-dependent solute transport at multiple levels of the renal tubule. These postglomerular vessels deliver less blood and, coupled with high oxygen consumption, leave the deeper medullary regions at the margin of hypoxemia. Vascular disorders that commonly threaten the blood supply of the kidney include large-vessel atherosclerosis, fibromuscular diseases, and embolic disorders. **Microvascular injury, including inflammatory and primary hematologic disorders, is described in Chap. 329.**

MECHANISMS OF VASCULAR INJURY AND HYPERTENSION

The glomerular capillary endothelium shares susceptibility to oxidative stress, pressure injury, and inflammation with other vascular territories. Endothelial injury can be manifest by urinary albumin excretion (UAE), which is predictive of systemic atherosclerotic disease events. Increased UAE may develop years before cardiovascular events. UAE and the risk of cardiovascular events are both reduced with pharmacologic therapy such as antihypertensive drugs and statins. Experimental studies demonstrate functional changes and rarefaction of renal microvessels under conditions of accelerated atherosclerosis and/or compromise of proximal perfusion pressures with large-vessel disease (Fig. 289-1).

Large-vessel renal artery occlusive disease can result from multiple conditions, including extrinsic compression of the vessel, intimal dissection, aortic stent graft placement, fibromuscular dysplasia (FMD), or, most commonly, atherosclerotic disease. Any disorder that reduces perfusion pressure to the kidney can activate mechanisms that tend to restore renal pressures at the expense of developing systemic hypertension. Because restoration of perfusion pressures can reverse these pathways, renovascular disease is considered a specifically treatable “secondary” cause of hypertension.

Renal artery stenosis is common, usually gradually progressive, and often has only minor hemodynamic effects. FMD is reported in 3–5% of normal subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but sometimes produces total occlusion and can be associated with renal artery aneurysms. Atherosclerotic renal artery stenosis (ARAS) is common in the general population (6.8% of a community-based sample above age 65). The prevalence increases with age and for patients with other vascular conditions such as coronary artery disease (18–23%) and/or peripheral aortic or lower

extremity disease (>30%). If untreated, ARAS progresses in nearly 50% of cases over a 5-year period, sometimes to total occlusion. Intensive treatment of arterial blood pressure and statin therapy can slow these rates and improve clinical outcomes.

Critical levels of stenosis (usually >70–80% luminal obstruction) lead to a reduction in perfusion pressure that activates the renin-angiotensin system, reduces sodium excretion, and activates sympathetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages, widely varying pressures, loss of circadian blood pressure (BP) rhythms, and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. It can also be treated with restoration of renal blood flow by either endovascular or surgical revascularization. Most patients require continued antihypertensive drug therapy due to preexisting hypertension and because revascularization alone rarely lowers BP to normal.

ARAS and systemic hypertension tend to affect both the poststenotic and contralateral kidneys, reducing overall glomerular filtration rate (GFR) in ARAS. When kidney function is threatened by large-vessel disease primarily, it has been labeled ischemic nephropathy. Moderately reduced blood flow that develops gradually is associated with reduced GFR and limited oxygen consumption with preserved tissue oxygenation. Hence, kidney function often remains reduced but stable during medical therapy, sometimes for years. With more advanced disease, reductions in cortical perfusion and overt tissue hypoxia develop. Unlike FMD, ARAS develops in patients with other risk factors for atherosclerosis and is commonly superimposed upon preexisting small-vessel disease in the kidney resulting from hypertension, aging, and diabetes. Nearly 85% of patients considered for renal revascularization have stage 3–5 chronic kidney disease (CKD) with estimated GFR <60 mL/min per 1.73 m². The presence of ARAS is a strong predictor of morbidity- and mortality-related cardiovascular events, independent of whether renal revascularization is undertaken.

DIAGNOSIS OF RENOVASCULAR DISEASE

Diagnostic approaches to renovascular disease necessarily include evaluation of the kidney vasculature and depend on the specific clinical questions to be addressed. Noninvasive characterization of the renal vasculature may be achieved by several techniques, summarized in **Table 289-1**. Although activation of the renin-angiotensin system is a key step in developing renovascular hypertension, it is transient. Levels of renin activity are therefore subject to timing, the effects of drugs, and sodium intake, and do not reliably predict the response to vascular therapy. Peak systolic renal artery velocities by Doppler ultrasound >200 cm/s generally predict lesions with more than >60% vessel lumen occlusion, although some treatment trials have required velocity >300 cm/s to avoid false positives. The renal resistive index has predictive value regarding the viability of the kidney. It remains operator- and institution-dependent, however. Contrast-enhanced computed tomography (CT) with vascular reconstruction provides excellent vascular images and functional assessment but carries a small risk of contrast toxicity. It provides a more reliable evaluation of accessory vessels and the distal vasculature than duplex or magnetic resonance imaging (MRI). Magnetic resonance angiography (MRA) is less often used than previously, as gadolinium contrast has been associated with nephrogenic systemic fibrosis particularly in patients with reduced GFR. Captopril-enhanced renography has a strong negative predictive value when entirely normal.

TREATMENT

Renal Artery Stenosis

While restoring renal blood flow and perfusion seems intuitively beneficial for high-grade occlusive lesions, revascularization procedures also pose hazards and expense. Patients with FMD are commonly younger females with otherwise normal vessels and a long

*Deceased

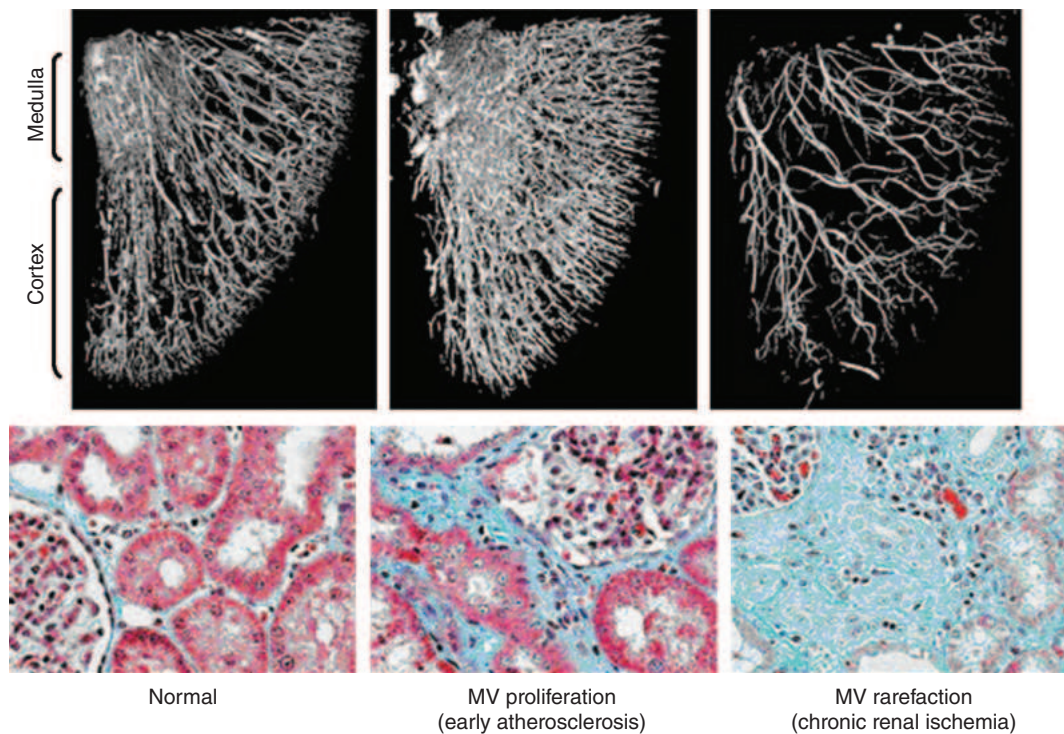


FIGURE 289-1 Examples of micro-CT images from vessels defined by radiopaque casts injected into the renal vasculature. These illustrate the complex, dense cortical capillary network supplying the kidney cortex that can either proliferate or succumb to rarefaction under the influence of atherosclerosis and/or occlusive disease. Changes in blood supply are followed by tubulointerstitial fibrosis and loss of kidney function. MV, microvascular. (Reproduced with permission from LO Lerman, AR Chade. *Angiogenesis in the kidney: A new therapeutic target?* *Curr Opin Nephrol Hypertens* 18:160, 2009.)

life expectancy. These patients often respond well to percutaneous renal artery angioplasty. If BP can be controlled to goal levels and kidney function remains stable in patients with ARAS, it may be argued that medical therapy with follow-up for disease progression is equally effective over periods of 3–5 years. Multiple prospective randomized controlled trials for individuals with moderate stenosis have failed to identify compelling additional benefits for interventional revascularization procedures regarding short-term results of BP and renal function. Studies of cardiovascular outcomes, including stroke, congestive heart failure, myocardial infarction, and end-stage renal failure, suggest a small mortality benefit for stented patients without proteinuria. Medical therapy should include blockade of the renin-angiotensin system, attainment of goal BPs, cessation of tobacco, statins, and aspirin. Follow-up requires surveillance for progressive occlusion manifest by worsening renal function

and/or loss of BP control. Renal revascularization should be considered for patients with rapidly progressive clinical syndromes, failing medical therapy, and/or developing additional complications. Techniques of renal revascularization are improving. With experienced operators, major complications occur in <5% of cases, including renal artery dissection, capsular perforation, hemorrhage, and occasional atheroembolic disease. Although not common, atheroembolic disease can be catastrophic and accelerate both hypertension and kidney failure, precisely the events that revascularization is intended to prevent. Although renal blood flow usually can be restored by endovascular stenting, recovery of renal function is limited to ~25% of cases, with no change in 50% and some deterioration evident in others. Patients with rapid loss of kidney function, sometimes associated with antihypertensive drug therapy, or with vascular disease affecting the entire functioning kidney mass

TABLE 289-1 Summary of Imaging Modalities for Evaluating the Kidney Vasculature			
Perfusion Studies to Assess Differential Renal Blood Flow			
Captopril renography with technetium-99m mertiatide (^{99m} Tc MAG3)	Captopril-mediated fall in filtration pressure amplifies differences in renal perfusion	Normal study excludes renovascular hypertension	Multiple limitations in patients with advanced atherosclerosis or creatinine >2.0 mg/dL (177 μmol/L)
Vascular Studies to Evaluate the Renal Arteries			
Duplex ultrasonography	Shows the renal arteries and measures flow velocity as a means of assessing the severity of stenosis	Inexpensive; widely available, suitable for follow-up studies	Heavily dependent on operator's experience; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia and abnormalities in accessory renal arteries
Computed tomographic angiography	Shows the renal arteries and perirenal aorta	Provides excellent images; stents do not cause artifacts	Expensive, moderate volume of contrast required
Magnetic resonance angiography	Shows the renal arteries and perirenal aorta	Not nephrotoxic, but concerns for gadolinium toxicity exclude use in GFR <30 mL/min/1.73 m ² ; provides excellent images	Expensive; gadolinium excluded in renal failure, unable to visualize stented vessels
Intraarterial angiography	Shows location and severity of vascular lesion	Considered "gold standard" for diagnosis of large-vessel disease, usually performed simultaneous with planned intervention	Expensive, associated hazard of atheroemboli, contrast toxicity, procedure-related complications, e.g., dissection

Abbreviation: GFR, glomerular filtration rate.

TABLE 289-2 Clinical Factors That Determine the Role of Revascularization in Addition to Medical Therapy for Renal Artery Stenosis**Factors Favoring Medical Therapy with Revascularization for Renal Artery Stenosis**

- Progressive decline in GFR during treatment of systemic hypertension
- Failure to achieve adequate blood pressure control with optimal medical therapy (medical failure)
- Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
- Decline in the GFR during therapy with ACE inhibitors or ARBs
- Recurrent congestive heart failure in a patient in whom left ventricular dysfunction does not fully explain the cause

Factors Favoring Medical Therapy and Surveillance of Renal Artery Disease

- Controlled blood pressure with stable renal function (e.g., stable renal insufficiency)
- Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound)
- Advanced age and/or limited life expectancy
- Extensive comorbidity that make revascularization too risky
- High risk for or previous experience with atheroembolic disease
- Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., interstitial nephritis, diabetic nephropathy), particularly with proteinuria

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate.

are more likely to recover function after restoring blood flow. When hypertension is refractory to effective therapy, revascularization offers real benefits. **Table 289-2** summarizes currently accepted guidelines for considering renal revascularization in addition to optimal medical therapy.

ATHEROEMBOLIC RENAL DISEASE

Emboli to the kidneys arise most frequently as a result of cholesterol crystals breaking free of atherosclerotic vascular plaque and lodging in downstream microvessels. Most clinical atheroembolic events follow angiographic procedures, often of the coronary vessels. It has been argued that nearly all arterial interventional procedures lead to plaque fracture and release of microemboli, but clinical manifestations develop only in a fraction of these. The incidence of clinical atheroemboli has been increasing with more vascular procedures and longer life spans. Atheroembolic renal disease is suspected in >3% of elderly subjects with end-stage renal disease (ESRD) and is likely underdiagnosed. It is more frequent in males with a history of diabetes, hypertension, and ischemic cardiac disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinically evident cases can be linked to precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy, or trauma. Clinical manifestations of this syndrome commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss, are present in less than half of patients, although cutaneous manifestations including livedo reticularis and localized toe gangrene may be more common. Worsening hypertension and deteriorating kidney function are common, sometimes reaching a malignant phase. Progressive renal failure can occur and require dialytic support. These cases often develop after a stuttering onset over many weeks and have an ominous prognosis. Mortality rate after 1 year exceeds 38%, and although some may eventually recover sufficiently to no longer require dialysis, many do not.

Beyond the clinical manifestations above, laboratory findings include rising creatinine, transient eosinophilia (60–80%), elevated sedimentation rate, and hypocomplementemia (15%). Establishing this diagnosis can be difficult and is often by exclusion. Definitive diagnosis depends on kidney biopsy demonstrating microvessel occlusion with

cholesterol crystals that leave a “cleft” in the vessel. Biopsies obtained from patients undergoing surgical revascularization of the kidney indicate that silent cholesterol emboli are frequently present before any further manipulation is performed.

No effective therapy is available for atheroembolic disease once it has developed. Withdrawal of anticoagulation is recommended. Late recovery of kidney function after supportive measures sometimes occurs, and statin therapy may improve outcome. The role of embolic protection devices in the renal circulation during angiography is unclear, but a few prospective trials have failed to demonstrate major benefits. The effect of such devices is limited to distal protection during the endovascular procedure, and they offer no protection from embolic debris developing after removal.

THROMBOEMBOLIC RENAL DISEASE

Thrombotic occlusion of renal vessels or branch arteries can lead to declining renal function and hypertension. It is difficult to diagnose and is often overlooked, especially in elderly patients. Thrombosis can develop as a result of local vessel abnormalities, such as local dissection, trauma, inflammatory vasculitis, or systemic infections, such as COVID-19. Local microdissections sometimes lead to patchy, transient areas of infarctions labeled “segmental arteriolar mediolysis.” Although hypercoagulability conditions sometimes present as renal artery thrombosis, this is rare. It can also derive from distant embolic events, e.g., the left atrium in patients with atrial fibrillation or from fat emboli originating from traumatized tissue, most commonly large bone fractures. Cardiac sources include vegetations from subacute bacterial endocarditis. Systemic emboli to the kidneys may also arise from the venous circulation if right-to-left shunting occurs, e.g., through a patent foramen ovale.

Clinical manifestations vary depending on the rapidity of onset and extent of occlusion. Acute arterial thrombosis may produce flank pain, fever, leukocytosis, nausea, and vomiting. If kidney infarction results, enzymes such as lactate dehydrogenase (LDH) rise transiently to extreme levels. If both kidneys are affected, renal function will decline precipitously with a drop in urine output. If a single kidney is involved, renal functional changes may be minor. Hypertension related to sudden release of renin from ischemic tissue can develop rapidly, as long as some viable tissue in the “peri-infarct” border zone remains. If the infarct zone demarcates precisely, the rise in BP and renin activity may resolve. Diagnosis of renal infarction may be established by vascular imaging with CT angiography, MRI, or arteriography (**Fig. 289-2**).

■ MANAGEMENT OF ARTERIAL THROMBOSIS OF THE KIDNEY

Options for interventions of newly detected arterial occlusion include surgical reconstruction, anticoagulation, thrombolytic therapy, endovascular procedures, and supportive care, particularly antihypertensive drug therapy. Application of these methods depends on the patient's overall condition, the precipitating factors (e.g., local trauma or systemic illness), the magnitude of renal tissue and function at risk, and the likelihood of recurrent events in the future. For unilateral disease, for example, arterial dissection with thrombosis and supportive care with anticoagulation may suffice. Acute, bilateral occlusion is potentially catastrophic, producing anuric renal failure. Depending on the precipitating event, surgical or thrombolytic therapies can sometimes restore kidney viability if undertaken early in the course of the acute event.

MICROVASCULAR INJURY ASSOCIATED WITH HYPERTENSION

■ ARTERIOLONEPHROSCLEROSIS

“Malignant” Hypertension Although BP rises with age, it has long been recognized that some individuals develop rapidly progressive BP elevations with target organ injury including retinal hemorrhages, encephalopathy, and declining kidney function. Placebo arms during the early controlled trials of hypertension therapy identified progression to severe levels in 20% of subjects over 5 years. If untreated, patients with target organ injury including papilledema

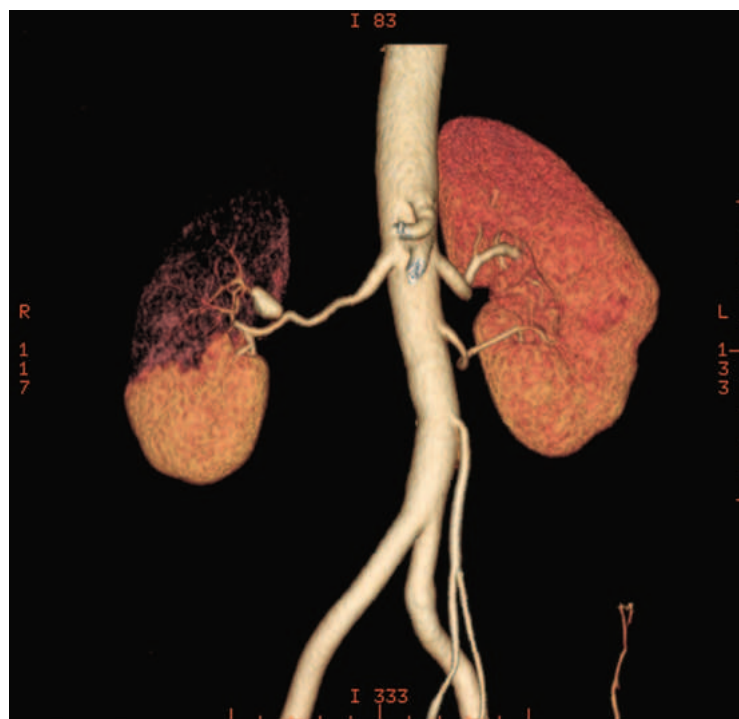
**A****B**

FIGURE 289-2 A. CT angiogram illustrating loss of circulation to the upper pole of the right kidney in a patient with fibromuscular disease and a renal artery aneurysm. Activation of the renin-angiotensin system produced rapidly developing hypertension. **B.** Angiogram illustrating high-grade renal artery stenosis affecting the left kidney. This lesion is often part of widespread atherosclerosis and sometimes is an extension of aortic plaque. This lesion develops in older individuals with preexisting atherosclerotic risk factors.

and declining kidney function suffered mortality rates in excess of 50% over 6–12 months, hence the designation “malignant.” Postmortem studies of such patients identified vascular lesions, designated “fibrinoid necrosis,” with breakdown of the vessel wall, deposition of eosinophilic material including fibrin, and a perivascular cellular infiltrate. A separate lesion was identified in the larger interlobular arteries in many patients with hyperplastic proliferation of the vascular wall cellular elements, deposition of collagen, and separation of layers, designated the “onionskin” lesion. For many of these

patients, fibrinoid necrosis led to obliteration of glomeruli and loss of tubular structures. Progressive kidney failure ensued and, without dialysis support, led to early mortality in untreated malignant-phase hypertension. These vascular changes could develop with pressure-related injury from a variety of hypertensive pathways, including but not limited to activation of the renin-angiotensin system and severe vasospasm associated with catecholamine release. Occasionally, endothelial injury is sufficient to induce microangiopathic hemolysis, as discussed below.

■ Non-disadvantaged: 0–119.2 ■ Non-disadvantaged: 119.2–173.1 ■ Non-disadvantaged: 173.1–227.5 ■ Non-disadvantaged: >227.5
 ■ Disadvantaged: 0–119.2 ■ Disadvantaged: 119.2–173.1 ■ Disadvantaged: 173.1–227.5 ■ Disadvantaged: >227.5

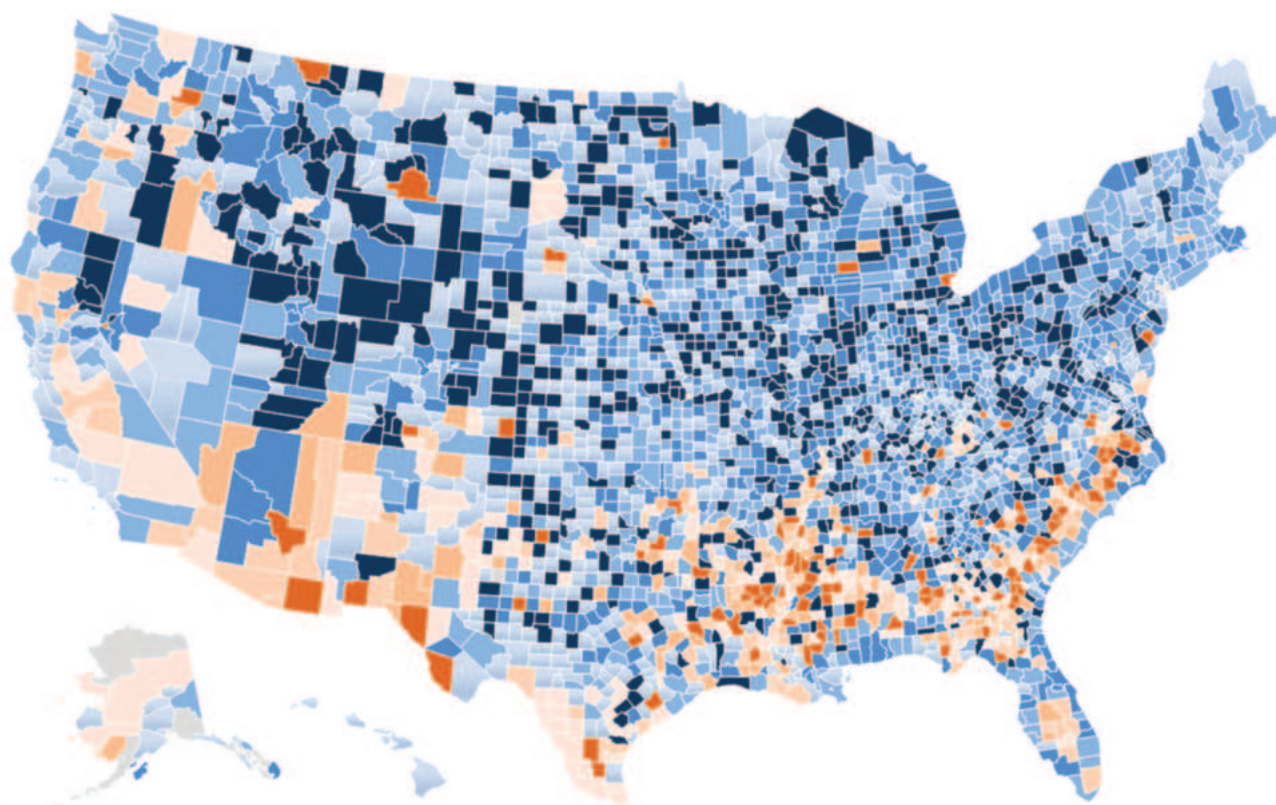


FIGURE 290-1 Observed hospitalizations for PE are shown per 100,000 Medicare beneficiaries aged 65 year or older residing in socioeconomically disadvantaged (orange) and nondisadvantaged (blue) counties of the United States in 2019. Lower hospitalization rates are represented with lighter shades of each color, and higher hospitalization rates are represented with darker shades. The range of hospitalizations per 100,000 represented by each shade of orange and each shade of blue are shown in the legend. (Reproduced with permission from RK Wadhera et al: *Circ Cardiovasc Qual Outcomes* 17:e010090, 2024.)

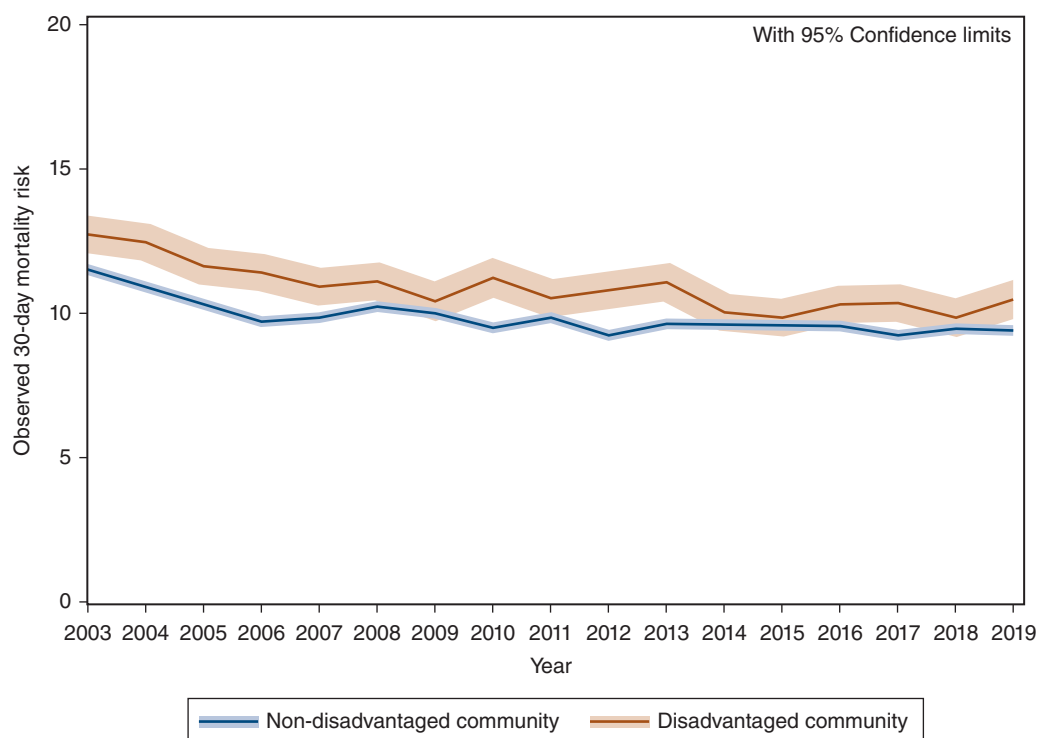


FIGURE 290-2 Trends in 30-day mortality among Medicare beneficiaries hospitalized with pulmonary embolism by community socioeconomic disadvantage from 2003 to 2019. The red lines represent beneficiaries from disadvantaged communities, and the blue line, beneficiaries from nondisadvantaged communities. The bands represent 95% confidence intervals for estimates. Trends in observed 30-day mortality among Medicare beneficiaries hospitalized with cardiovascular conditions by community socioeconomic disadvantage from 2003 to 2019. (Reproduced with permission from RK Wadhera et al: *Circ Cardiovasc Qual Outcomes* 17:e010090, 2024.)

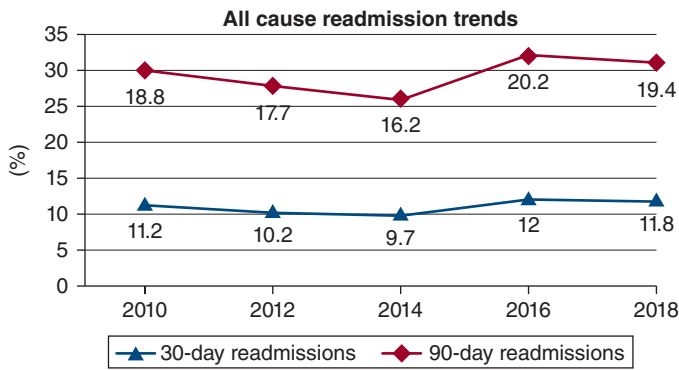


FIGURE 290-3 Graph showing all-cause readmission rates for pulmonary embolism (PE) patients within 30 days and within 90 days from 2010 to 2018. (Reproduced from M Murthi: *Am J Cardiol* 184:133, 2022.)

Postthrombotic Syndrome Postthrombotic syndrome (also known as *chronic venous insufficiency*) damages the venous valves of the leg and worsens quality of life by causing ankle or calf swelling and leg aching, especially after prolonged standing. In its most severe form, postthrombotic syndrome causes deep skin ulceration (Fig. 290-6).

PATHOPHYSIOLOGY

Inflammation Inflammation takes center stage as a trigger of acute PE and DVT. Inflammation-related risk factors and medical illnesses are now linked as precipitants of VTE (Table 290-1).

Prothrombotic States The two most common autosomal dominant genetic mutations are (1) factor V Leiden, which causes resistance to the endogenous anticoagulant, protein C, and (2) the prothrombin gene mutation, which increases the plasma prothrombin concentration (Chaps. 69 and 122). Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors. Deficiencies of these inhibitors

are associated with VTE but are rare. Antiphospholipid syndrome (APS) is an acquired (not genetic) thrombophilic disorder that predisposes to both venous and arterial thrombosis. Patients with APS often warrant lifetime anticoagulation, even if the initial VTE was provoked by trauma or surgery.

Clinical Risk Factors Common comorbid VTE risk factors include cancer, obesity, cigarette smoking, systemic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, long-haul air travel, air pollution, estrogen-containing contraceptives, pregnancy, the first 6–12 weeks postpartum, postmenopausal hormone replacement, surgery, and trauma. A sedentary lifestyle is an increasingly prevalent risk factor. A Japanese study found that each 2 hours per day increment of television watching is associated with a 40% increased likelihood of fatal PE.

Polygenic Risk Scores Ghouse and colleagues reported a genome-wide association study of VTE that incorporated 81,190 cases and 1,419,671 controls from six cohorts. They identified 93 risk loci, 62 of which were previously unreported. Many risk loci affected the coagulation cascade or platelet function. A VTE *polygenic risk score* (PRS) enabled identification of both high- and low-risk individuals. Individuals within the top 0.1% of PRS distribution had a VTE risk similar to homozygous or compound heterozygous carriers of factor V Leiden or the prothrombin gene mutation. In contrast, in the bottom 10% of the PRS distribution, factor V Leiden and prothrombin gene mutation carriers had a VTE risk similar to that of the general population. PRS improved individual risk prediction beyond that of genetic and clinical risk factors. Some risk factors for arterial thrombosis, such as body mass index and smoking, were concordant with VTE risk, whereas others, such as blood pressure and triglyceride levels, were discordant.

Activated Platelets Virchow's triad of venous stasis, hypercoagulability, and endothelial injury, usually coupled with an inflammatory trigger, leads to recruitment of activated platelets, which release microparticles. These microparticles contain proinflammatory mediators

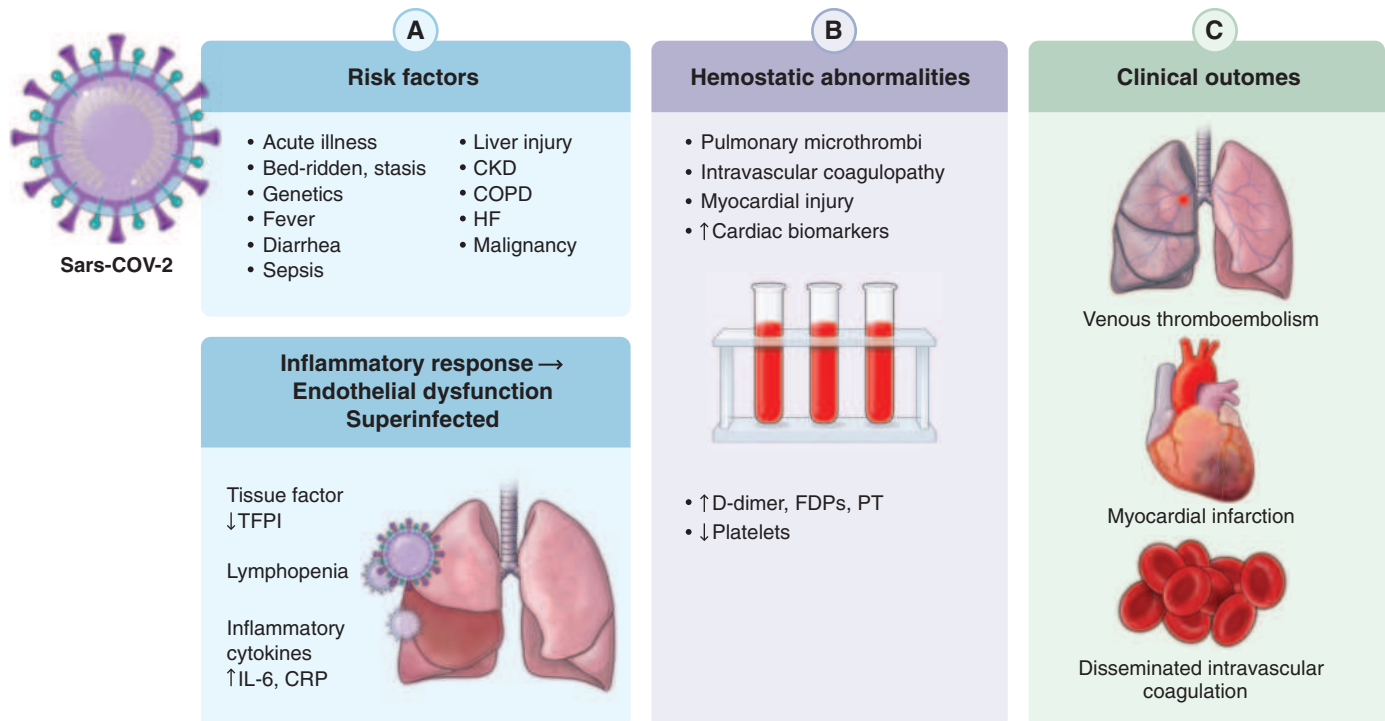


FIGURE 290-4 Postulated mechanisms of coagulopathy and pathogenesis of thrombosis in COVID-19. **A.** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection activates an inflammatory response, leading to release of inflammatory mediators. Endothelial and hemostatic activation ensues, with decreased levels of TFPI and increased tissue factor. The inflammatory response to severe infection is marked by lymphopenia and thrombocytopenia. Liver injury may lead to decreased coagulation and antithrombin formation. **B.** COVID-19 may be associated with hemostatic derangement and elevated troponin. **C.** Increased thromboembolic state results in venous thromboembolism, myocardial infarction, or, in case of further hemostatic derangement, disseminated intravascular coagulation. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FDP, fibrin degradation product; HF, heart failure; IL, interleukin; LDH, lactate dehydrogenase; PT, prothrombin time; TFPI, tissue factor pathway inhibitor. (Reproduced with permission from B Bikdeli et al: *COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up*. *J Am Coll Cardiol* 75:2950, 2020.)

PVFS scale grade	Description
0	No functional limitations All usual duties/activities at home or at work can be carried out at the same level of intensity. Symptoms, pain and anxiety are absent.
1	Negligible functional limitations All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain, or anxiety.
2	Slight functional limitations Some usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety.
3	Moderate functional limitations Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain, or anxiety.
4	Severe functional limitations Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required.
D	Death Death occurred before the scheduled assessment.

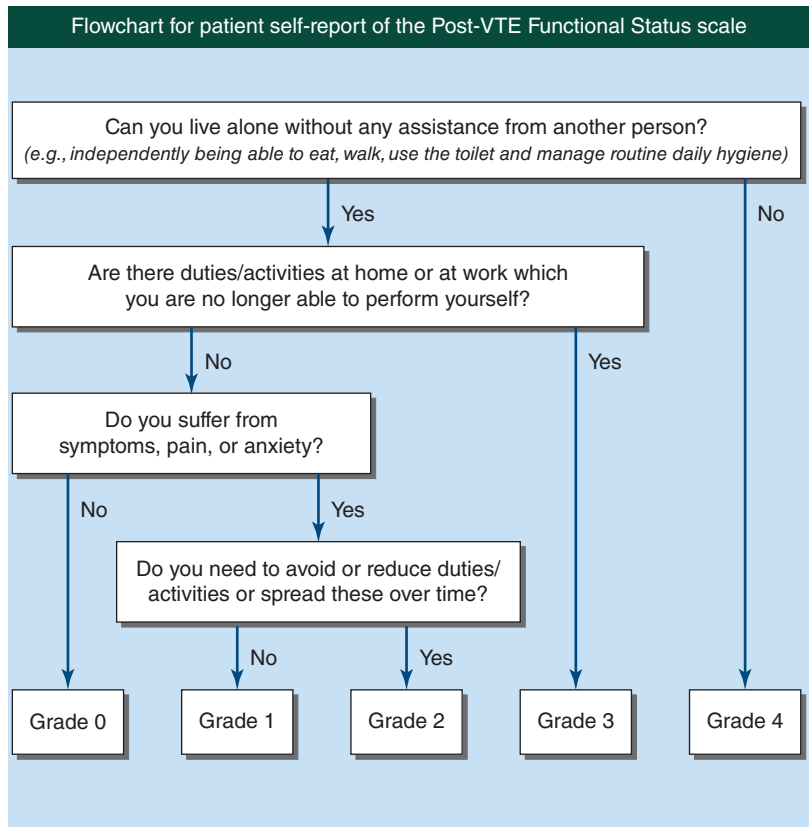


FIGURE 290-5 Flow chart for patient self-report of the Post-Venous Thromboembolism (VTE) Functional Status scale. (Reproduced with permission from GJAM Boon et al: *Thromb Res* 190:45, 2020, Figure 2.)

that bind neutrophils, stimulating them to release their nuclear material and form web-like extracellular networks called *neutrophil extracellular traps*. These prothrombotic networks contain histones that stimulate platelet aggregation and promote platelet-dependent thrombin

generation. Venous thrombi form and flourish in this environment of stasis, low oxygen tension, and upregulation of proinflammatory genes.

Interaction Between Venous Thromboembolism and Atherothrombosis VTE (red clot) and arterial thrombotic (white clot) events were previously considered separate entities. However, the presence of carotid artery plaque is associated with double the risk of incident VTE. This observation led to the discovery of a broad interaction of VTE with acute coronary syndrome and with acute ischemic stroke (Fig. 290-7). These three vascular conditions share similar risk factors and similar pathophysiology: inflammation, hypercoagulability, and endothelial injury. Patients who suffer VTE are more than twice



FIGURE 290-6 Skin ulceration in the medial malleolus from postthrombotic syndrome of the leg.

TABLE 290-1 Inflammation-Linked Conditions That Can Trigger PE or DVT

Ulcerative colitis
Crohn's disease
Rheumatoid arthritis
Psoriasis
Diabetes mellitus, type 2
Obesity/metabolic syndrome
Hypercholesterolemia, especially elevated LDL cholesterol
Lipoprotein(a)
Pneumonia
Acute coronary syndrome
Acute stroke
Cigarette smoking
Sepsis/septic shock
Erythropoiesis-stimulating agents
Blood transfusion
Cancer

Abbreviations: DVT, deep-venous thrombosis; LDL, low-density lipoprotein; PE, pulmonary embolism.

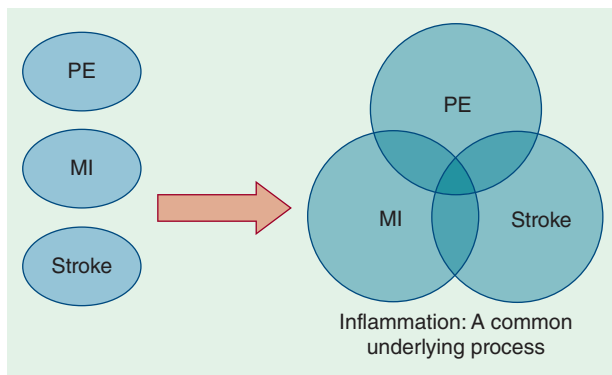


FIGURE 290-7 Broad interaction between venous thromboembolism and atherothrombosis. MI, myocardial infarction; PE, pulmonary embolism.

as likely to have a future MI or stroke. Conversely, patients with MI or stroke are more than twice as likely to suffer a future VTE.

Embolization When DVTs (Fig. 290-8) detach from their site of formation, they embolize to the vena cava, right atrium, and right ventricle and lodge in the pulmonary arterial circulation, thereby causing acute PE. Many patients with PE have no evidence of DVT because the leg thrombus has already embolized to the lungs. Paradoxically, these thrombi occasionally embolize to the arterial circulation through a patent foramen ovale or atrial septal defect.

Physiology The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial O_2 tension gradient, which represent the inefficiency of oxygen transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries (Fig. 290-9).

Other pathophysiologic abnormalities include:

1. *Increased pulmonary vascular resistance* due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin. Release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial O_2 gradient.
2. *Impaired gas exchange* due to increased alveolar dead space from vascular obstruction, hypoxemia from alveolar hypoventilation relative to perfusion in the nonobstructed lung, right-to-left shunting, or impaired carbon monoxide transfer due to loss of gas exchange surface.
3. *Alveolar hyperventilation* due to reflex stimulation of irritant receptors.

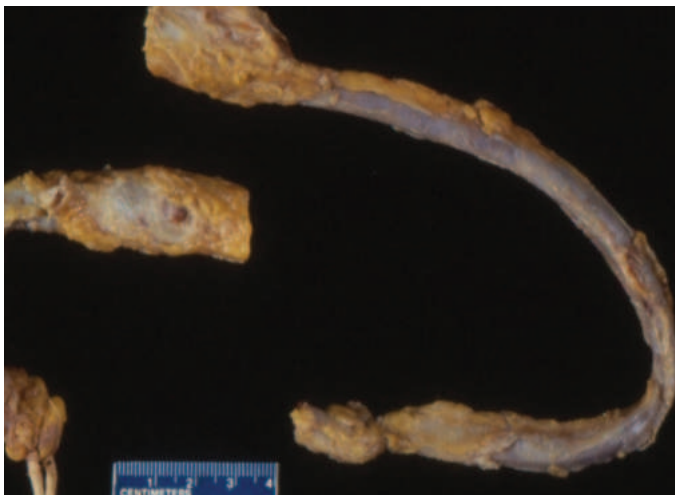


FIGURE 290-8 Deep-venous thrombosis at autopsy.

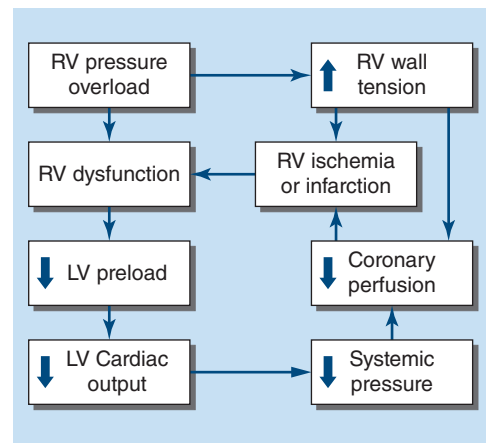


FIGURE 290-9 Pathophysiology of pulmonary embolism (PE). LV, left ventricular; RV, right ventricular.

4. *Increased airway resistance* due to constriction of airways distal to the bronchi.
5. *Decreased pulmonary compliance* due to lung edema, lung hemorrhage, or loss of surfactant.

Pulmonary Hypertension, Right Ventricular (RV) Dysfunction, and RV Microinfarction Pulmonary artery obstruction and neurohumoral mediators cause a rise in both pulmonary artery pressure and pulmonary vascular resistance. When RV wall tension rises, RV dilation, stretch, and dysfunction ensue, with release of the cardiac biomarker brain natriuretic peptide. The interventricular septum bulges into and compresses an intrinsically normal left ventricle (LV). Diastolic LV dysfunction reduces LV distensibility and impairs LV filling. Increased RV wall tension also compresses the right coronary artery, limits myocardial oxygen supply, and precipitates right coronary artery ischemia and RV microinfarction, with release of cardiac biomarkers such as troponin. Underfilling of the LV may lead to a fall in LV cardiac output and systemic arterial pressure, with consequent circulatory collapse and death (Fig. 290-9).

■ CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP-VEIN THROMBOSIS

Pulmonary Embolism *Massive (high-risk) PE* accounts for 5–10% of cases and is usually characterized by systemic arterial hypotension and extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure. *Submassive (intermediate-risk) PE* accounts for 20–25% of patients and is characterized by RV dysfunction despite normal systemic arterial pressure. The combination of right heart failure and release of cardiac biomarkers such as troponin indicates a high risk of clinical deterioration. *Low-risk PE* constitutes about 65–75% of cases. These patients have an excellent prognosis.

Deep-Venous Thrombosis *Lower extremity DVT* usually begins in the calf and can propagate proximally to the popliteal, femoral, and iliac veins. Leg DVT is ~10 times more common than *upper extremity DVT*, which is often precipitated by placement of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters. The likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase.

Superficial venous thrombosis usually presents with erythema, tenderness, and a “palpable cord”; it is most common in the lower extremities because of varicose veins and in the upper extremities because of indwelling intravenous catheters. Superficial veins may be visible in the chest wall (*Urschel’s sign*). Patients are at risk for extension of the superficial vein thrombosis to the deep-venous system.

DIAGNOSIS

Clinical Evaluation PE is known as “the great masquerader.” Diagnosis is difficult because symptoms and signs are nonspecific.

The most common symptom of PE is unexplained breathlessness. When occult PE occurs concomitantly with overt congestive heart failure or pneumonia, clinical improvement often fails to ensue despite standard medical treatment of the concomitant illness. This scenario provides a clinical clue to the possible coexistence of PE.

With DVT, the most common symptom is a cramp or “charley horse” in the lower calf that persists and intensifies over several days. Wells Point Score criteria, validated in ambulatory patients but not in hospitalized patients, help estimate the clinical likelihood of DVT and PE (Table 290-2). Patients with a low likelihood of DVT or a low-to-moderate likelihood of PE should undergo initial diagnostic evaluation with D-dimer testing alone (see “Blood Tests”), without obligatory imaging tests if the D-dimer test result is normal (Fig. 290-10). However, patients with a high clinical likelihood of VTE should skip D-dimer testing and undergo imaging as the next step in the diagnostic algorithm.

Clinical Pearls Not all leg pain is due to DVT, and not all dyspnea is due to PE (Table 290-3). Sudden, severe calf discomfort suggests a ruptured Baker’s cyst. Fever and chills often herald cellulitis rather than DVT. Physical findings, if present, may consist only of mild palpation discomfort in the lower calf. However, massive DVT often presents with marked thigh swelling, tenderness, and erythema. If a leg is diffusely edematous, DVT is unlikely, except for the most serious form of DVT, *phlegmasia cerulea dolens*. Recurrent left thigh edema, especially in young women, raises the possibility of May-Thurner syndrome, with right proximal iliac artery compression of the left proximal iliac vein. This syndrome may be associated with a DVT. Upper extremity venous thrombosis may present with asymmetry in the supraclavicular fossa or in the circumference of the upper arms.

Pulmonary infarction usually indicates a small PE. This condition is exquisitely painful because the thrombus lodges peripherally, near the innervation of pleural nerves. *Nonthrombotic PE* etiologies include fat embolism after pelvic or long bone fracture, tumor embolism, bone marrow, and air embolism. Cement embolism and bony fragment embolism can occur after total hip or knee replacement. Intravenous drug users may inject themselves with a wide array of substances that

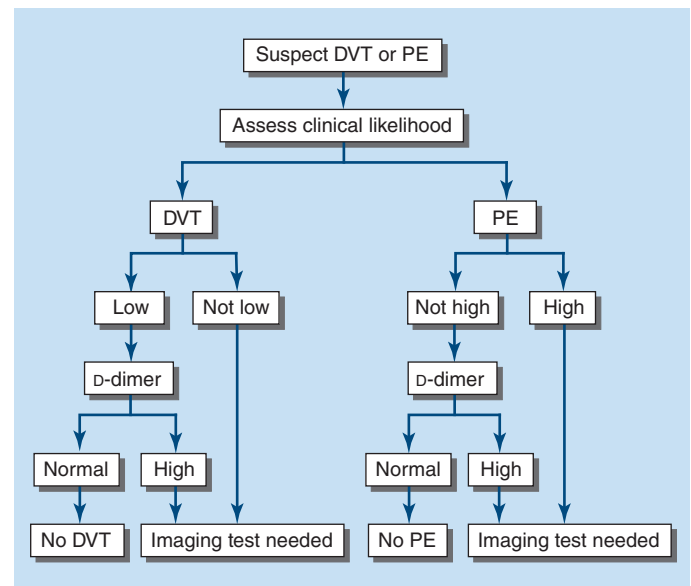


FIGURE 290-10 How to decide whether diagnostic imaging is needed. For assessment of clinical likelihood, see Table 290-2. DVT, deep-venous thrombosis; PE, pulmonary embolism.

can embolize, such as hair, talc, and cotton. *Amniotic fluid embolism* occurs when fetal membranes leak or tear at the placental margin.

Nonimaging Diagnostic Modalities • **BLOOD TESTS** The quantitative *plasma D-dimer enzyme-linked immunosorbent assay (ELISA)* rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin. Elevation of D-dimer indicates endogenous, although often clinically ineffective, thrombolysis. The sensitivity of an abnormally elevated D-dimer is >95% for PE. A normal D-dimer is a useful “rule out” test for PE in patients with low pretest probability. However, the D-dimer assay is not specific. Levels increase in patients with MI, pneumonia, sepsis, cancer, and the postoperative state, and those in the second or third trimester of pregnancy. Therefore, D-dimer testing rarely has a useful role among hospitalized patients because levels are frequently elevated due to systemic illness.

The upper limit of normal for D-dimer was considered to be 500 ng/mL; however, guidelines now recommend use of an age-adjusted D-dimer when ruling out acute PE. The age-adjusted D-dimer applies to patients older than 50 years of age with low or intermediate clinical probability of PE. To calculate the upper limit of normal D-dimer in these patients, multiply the age by 10. For example, a 70-year-old patient suspected of PE would have 700 ng/mL as the upper limit of normal for D-dimer. Implementing routine use of the

TABLE 290-2 Clinical Decision Rules

Low Clinical Likelihood of DVT if Point Score Is Zero or Less; Moderate Likelihood if Score Is 1 to 2; High Likelihood if Score Is 3 or Greater	
CLINICAL VARIABLE	DVT SCORE
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	−2
High Clinical Likelihood of PE if Point Score Exceeds 4	
CLINICAL VARIABLE	PE SCORE
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Abbreviations: DVT, deep-venous thrombosis; PE, pulmonary embolism.

TABLE 290-3 Differential Diagnosis of DVT and PE

DVT
Ruptured Baker’s cyst
Muscle strain/injury
Cellulitis
Acute postthrombotic syndrome/venous insufficiency
PE
Pneumonia, asthma, chronic obstructive pulmonary disease
Congestive heart failure
Pericarditis
Pleurisy: “viral syndrome,” costochondritis, musculoskeletal discomfort
Rib fracture, pneumothorax
Acute coronary syndrome
Anxiety
Vasovagal syncope

Abbreviations: DVT, deep-venous thrombosis; PE, pulmonary embolism.

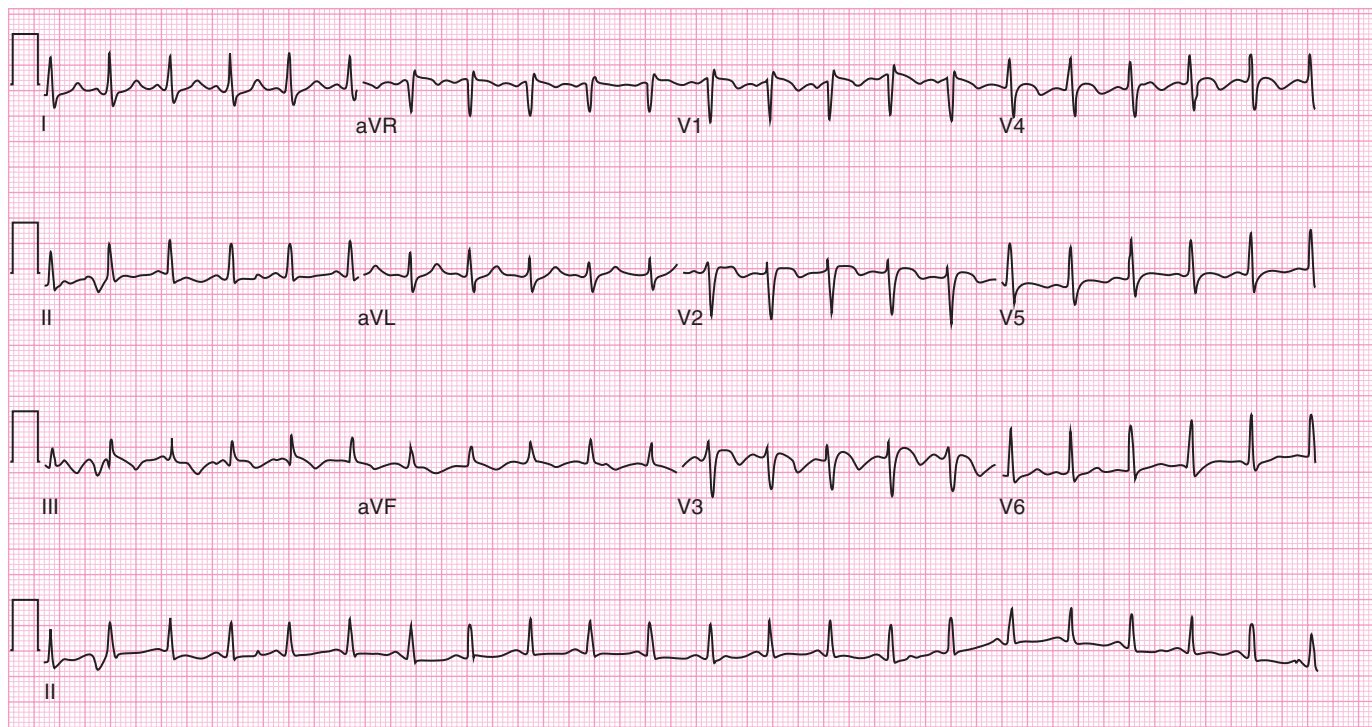


FIGURE 290-11 Electrocardiogram with both the S1Q3T3 sign and T-wave inversions in leads V₁-V₄—typical of an anatomically large pulmonary embolism. This patient's CT pulmonary angiogram is shown as Fig. 290-13A and B.

age-adjusted D-dimer reduces the number of computed tomography (CT) pulmonary angiograms that are ordered. However, the age-adjusted D-dimer does not apply to patients suspected of acute DVT.

ELEVATED CARDIAC BIOMARKERS Serum troponin increases because of RV microinfarction. Myocardial stretch causes release of brain natriuretic peptide or NT-pro-brain natriuretic peptide.

ELECTROCARDIOGRAM The most frequently cited abnormality, in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III (Chap. 247). This finding is relatively specific but insensitive. RV strain and ischemia cause the most common abnormality, T-wave inversion in leads V₁ to V₄ (Fig. 290-11).

Noninvasive Imaging Modalities • **VENOUS ULTRASONOGRAPHY** Ultrasonography of the deep-venous system relies on loss of vein compressibility as the primary diagnostic criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure on the ultrasound transducer. This creates the illusion

of a “wink.” With acute DVT, the vein loses its compressibility because of passive distention by acute thrombus. The diagnosis of acute DVT is even more secure when thrombus is directly visualized; it appears homogeneous, is located in the center of the vein, and has low echogenicity (Fig. 290-12). The vein itself often appears mildly dilated, and collateral channels may be absent.

Venous flow dynamics can be examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by an obstructing DVT or by any obstructive process within the pelvis. For patients with a technically poor or nondiagnostic venous ultrasound, consider alternative imaging modalities such as CT and magnetic resonance imaging.

CHEST ROENTGENOGRAPHY A normal or nearly normal chest x-ray often occurs in PE. Well-established abnormalities include focal oligemia (*Westermarck's sign*), a peripheral triangular-shaped density usually located at the pleural base (*Hampton's hump*—which is usually due to pulmonary infarction), and an enlarged right descending pulmonary artery (*Palla's sign*).

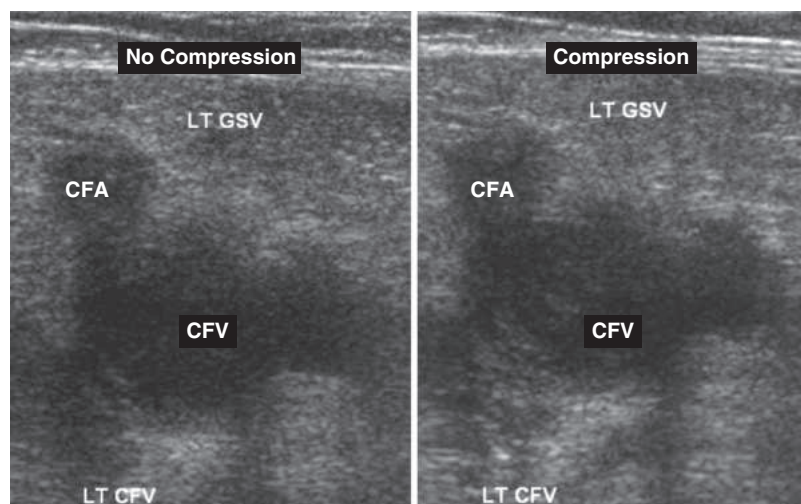


FIGURE 290-12 Venous ultrasound, with and without compression of the leg veins. CFA, common femoral artery; CFV, common femoral vein; GSV, great saphenous vein; LT, left.

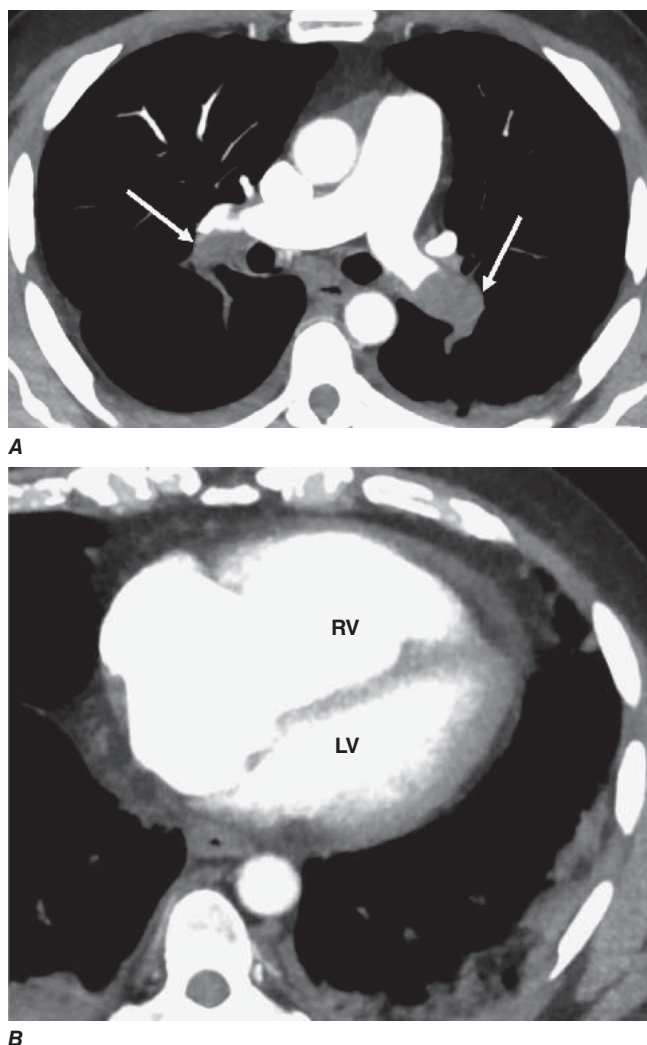


FIGURE 290-13 **A.** Massive bilateral proximal pulmonary embolism on an axial chest CT image in a 53-year-old man (whose electrocardiogram is shown in Fig. 290-11) with filling defects in the right and left main pulmonary arteries (white arrows). **B.** Four-chamber view in the same patient showing the right ventricle (RV) larger than the left ventricle (LV).

CHEST CT CT pulmonary angiography with intravenous contrast is the principal imaging test for the diagnosis of PE (Fig. 290-13A). Thin-cut chest CT images can provide exquisite detail, with ≤ 1 mm of resolution during a short breath hold. Sixth-order branches can be visualized with resolution superior to that of conventional invasive contrast pulmonary angiography. The CT scan also provides an excellent four-chamber view of the heart (Fig. 290-13B). RV enlargement on chest CT indicates an increased likelihood of death within the next 30 days compared with PE patients who have normal RV size (commonly defined as a right to left ventricular diameter ratio >1). In patients without PE, the lung parenchymal images may establish alternative diagnoses not apparent on chest x-ray that explain the presenting symptoms and signs, such as pneumonia, emphysema, pulmonary fibrosis, pulmonary mass, and aortic pathology.

LUNG SCANNING Ventilation/perfusion lung scanning has become a second-line diagnostic test for PE, used mostly for patients who cannot tolerate intravenous contrast. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected intravenously and trapped in the pulmonary capillary bed. The perfusion scan defect indicates absent or decreased blood flow, possibly due to PE. Ventilation scans, obtained with a radiolabeled inhaled gas such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal nonventilated lung, thereby providing possible explanations for perfusion defects other than acute PE, such as asthma or chronic obstructive pulmonary disease. A high-probability

scan for PE is defined as two or more segmental perfusion defects in the presence of normal ventilation. The diagnosis of PE is very unlikely in patients with normal and nearly normal scans and, in contrast, is $\sim 90\%$ certain in patients with high-probability scans.

MAGNETIC RESONANCE (MR) (CONTRAST-ENHANCED) IMAGING When pelvic or leg ultrasound is equivocal, MR venography with gadolinium contrast is an excellent imaging modality to diagnose DVT. MR pulmonary angiography may detect large proximal PE but is not reliable for smaller segmental and subsegmental PE.

ECHOCARDIOGRAPHY Echocardiography is *not* a reliable diagnostic imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is very useful for detecting conditions that may mimic PE, such as acute MI, pericardial tamponade, and aortic dissection. Transthoracic echocardiography rarely images thrombus directly in the main pulmonary artery or the right or left main branches. The best-known indirect sign of PE on transthoracic echocardiography is McConnell's sign: hypokinesia of the RV free wall with normal or hyperkinetic motion of the RV apex.

Invasive Diagnostic Modalities • **PULMONARY ANGIOGRAPHY** Chest CT pulmonary angiography with contrast (see above) has virtually replaced invasive pulmonary angiography as a diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs and for those in whom an interventional procedure such as catheter-directed thrombolysis or embolectomy is planned. A definitive diagnosis of PE requires visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion ("cut-off") of vessels, segmental oligemia, avascularity, and a prolonged arterial phase with slow filling and tortuous, tapering peripheral vessels.

CONTRAST PHLEBOGRAPHY Venous ultrasonography has virtually replaced contrast phlebography as the principal diagnostic test for suspected DVT. However, contrast phlebography is used when an interventional procedure is planned.

Integrated Diagnostic Approach An integrated diagnostic approach streamlines the workup of suspected DVT and PE (Fig. 290-14).

TREATMENT

Deep-Venous Thrombosis

UPPER EXTREMITY DVT

As peripherally inserted central catheter (PICC) use has increased, so has the rate of upper extremity DVT. This rate can be decreased by more judicious selection of patients who require a PICC, use of single-lumen rather than double- or triple-lumen PICCs, and use of the smallest possible lumen size, ideally 4 French rather than 5 or 6 French.

ISOLATED CALF DVT

The GARFIELD-VTE Registry recruited 2145 patients with isolated calf DVT and 3846 patients with proximal DVT with or without calf DVT. Isolated calf DVT patients were more likely to have either undergone surgery or have experienced leg trauma, and they were less likely to have active cancer or a prior history of VTE. Almost all isolated calf DVT patients received anticoagulation, and nearly half were anticoagulated for at least 1 year.

FIBRINOLYSIS

If advanced therapy beyond anticoagulation is warranted, one can utilize clot dissolution or clot extraction therapy with catheter-directed therapy. The open vein hypothesis postulates that patients who receive primary therapy will sustain less long-term damage to venous valves, with consequent lower rates of postthrombotic syndrome. However, the ATTRACT trial randomized 692 patients with femoral or iliofemoral DVT to catheter-directed therapy plus

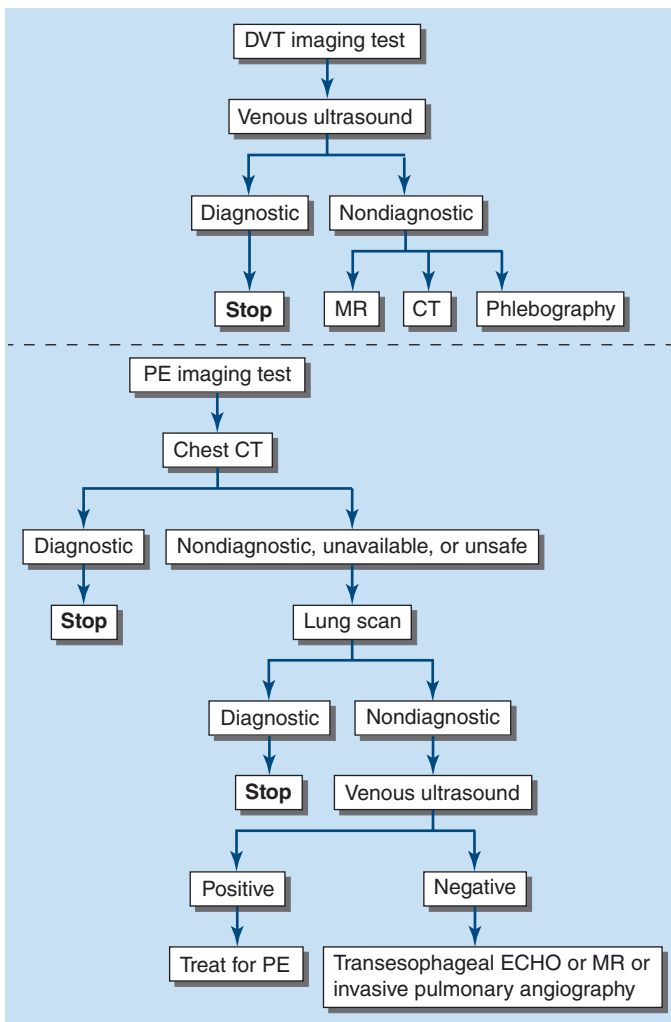


FIGURE 290-14 Integrated diagnostic approach. CT, computed tomography; DVT, deep-venous thrombosis; ECHO, echocardiography; MR, magnetic resonance; PE, pulmonary embolism.

anticoagulation versus usual care with anticoagulation alone. After 2 years of follow-up, there was no overall reduction in postthrombotic syndrome in the thrombolysis group. However, there was a trend toward less postthrombotic syndrome among patients with iliofemoral DVT (compared with only femoral DVT) who received catheter-directed thrombolysis compared with anticoagulation alone.

COMPRESSION STOCKINGS

For patients with swelling of the legs when acute DVT is diagnosed, below-knee graduated compression stockings may be prescribed, usually 30–40 mmHg or 20–30 mmHg, to lessen patient discomfort. They should be replaced every 3–6 months because they lose their elasticity. However, prescription of vascular compression stockings in asymptomatic newly diagnosed acute DVT patients does not prevent the development of postthrombotic syndrome.

TREATMENT

Pulmonary Embolism

RISK STRATIFICATION

Hemodynamic instability, RV dysfunction on echocardiography, RV enlargement on chest CT, and elevation of the troponin level due to RV microinfarction portend a high risk of adverse clinical outcomes despite anticoagulation. However, in most cases, RV

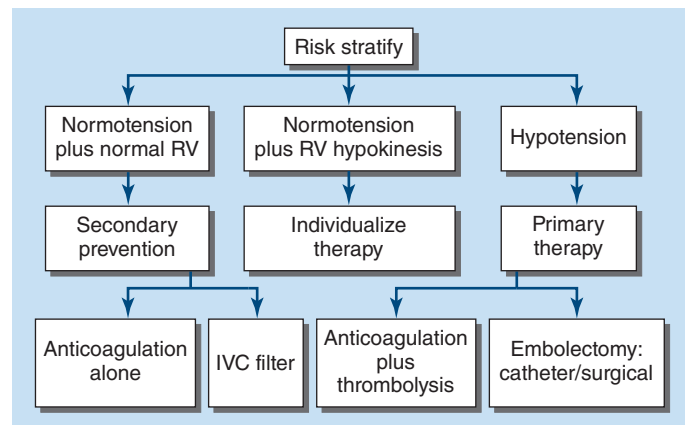


FIGURE 290-15 Acute management of pulmonary thromboembolism. IVC, inferior vena cava; PE, pulmonary embolism; RV, right ventricular.

function and hemodynamic function remain normal, which portend an excellent prognosis and clinical outcome (Fig. 290-15).

ANTICOAGULATION

There are three major strategies for anticoagulation: (1) the well-established—but waning—strategy of parenteral anticoagulation with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux either as monotherapy or more often “bridged” to warfarin; (2) parenteral anticoagulation, switched after 5 days to dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent); or (3) oral anticoagulation monotherapy with rivaroxaban or apixaban (both anti-Xa agents) with a 3-week or 1-week loading dose, respectively. For patients with VTE in the setting of suspected or proven heparin-induced thrombocytopenia, one can choose between two intravenous direct thrombin inhibitors: argatroban (metabolized by the liver) or bivalirudin (metabolized by the kidney), or subcutaneously administered fondaparinux (Table 290-4).

Unfractionated Heparin UFH binds to and accelerates the activity of antithrombin, thus preventing additional thrombus formation. Intravenous UFH is typically dosed to achieve a target activated partial thromboplastin time (aPTT) of 60–80 s, which usually corresponds to a chromogenic anti-Xa level of 0.3–0.7 U/mL. When switching from a direct oral anticoagulant (DOAC) to intravenous UFH, monitor the aPTT, not the chromogenic anti-Xa assay. However, the anti-Xa assay is more accurate than the aPTT in critically ill patients, APS, pregnancy, and suspected heparin resistance.

In patients with normal liver function, use an initial bolus of 80 U/kg as a loading dose of UFH, followed by an initial infusion rate of 18 U/kg per h in patients with normal liver function. The short half-life of UFH is especially useful in patients in whom hour-to-hour control of anticoagulation intensity is desired. Heparin also has pleiotropic effects that may decrease systemic and local inflammation.

Low-Molecular-Weight Heparins These fragments of UFH exhibit less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease.

Fondaparinux Fondaparinux, an anti-Xa pentasaccharide, is essentially an ultra-low-molecular-weight heparin. It is administered as a weight-based, once-daily subcutaneous injection in a pre-filled syringe. No laboratory monitoring is required. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia. For patients with renal dysfunction, the fondaparinux dose must be adjusted downward.

TABLE 290-4 Anticoagulation of VTE

Non-Warfarin Anticoagulation

Unfractionated heparin, bolus and continuous infusion, to achieve aPTT 2–3 times the upper limit of the laboratory normal, *or*

Enoxaparin 1 mg/kg twice daily with normal renal function, *or*

Dalteparin 200 U/kg once daily or 100 U/kg twice daily, with normal renal function, *or*

Tinzaparin 175 U/kg once daily with normal renal function, *or*

Fondaparinux weight-based once daily; adjust for impaired renal function

Direct thrombin inhibitors: argatroban or bivalirudin (with suspected or proven heparin-induced thrombocytopenia)

Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily with the dinner meal thereafter. For CrCl 15–50 mL/min: 10 mg twice daily.

Apixaban 10 mg twice daily for 1 week, followed by 5 mg twice daily thereafter. In patients with at least 2 of the following characteristics: age >80 years, body weight <60 kg, or serum creatinine >1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily.

Dabigatran: 5 days of unfractionated heparin, LMWH, or fondaparinux followed by dabigatran 150 mg twice daily with CrCl >30 mL/min. For CrCl 15–30 mL/min: 75 mg twice daily.

Edoxaban: 5 days of unfractionated heparin, LMWH, or fondaparinux followed by edoxaban 60 mg once daily with normal renal function, weight >60 kg, in the absence of potent P-glycoprotein inhibitors. For CrCl 15–50 mL/min: 30 mg once daily.

Warfarin Anticoagulation

Requires 5–10 days of administration to achieve effectiveness as monotherapy

Use full-dose unfractionated heparin, LMWH, or fondaparinux as “bridging agents” when initiating warfarin. Continue parenteral anticoagulation for a minimum of 5 days and until two sequential INR values, at least 1 day apart, achieve the target INR range.

Usual start dose is 5 mg

Titrate to INR, target 2.0–3.0

Abbreviations: aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; INR, international normalized ratio; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

Warfarin This vitamin K antagonist prevents carboxylation-dependent activation of coagulation factors II, VII, IX, and X (Chap. 69). The full effect of warfarin is attained after daily therapy for 5–7 days. Overlapping UFH, LMWH, fondaparinux, or parenteral direct thrombin inhibitors during initiation of warfarin provides therapeutic levels of anticoagulation. Parenteral anticoagulation is discontinued when warfarin has achieved a target international normalized ratio (INR) of 2.5. Warfarin can cause major hemorrhage, including intracranial hemorrhage, even when the INR remains within the desired therapeutic range. Warfarin can also cause “off-target” side effects such as alopecia or arterial vascular calcification. Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Some patients can self-monitor their INR with a home point-of-care fingerstick machine, and a few can be taught to self-dose their warfarin.

Direct Oral Anticoagulants DOACs are administered in a fixed dose, establish effective anticoagulation within hours of ingestion, do not require laboratory coagulation monitoring or limitation of green leafy vegetables, and have few drug-drug interactions. DOACs should not be prescribed during pregnancy or breastfeeding. Warfarin, not DOACs, is the standard treatment for APS. The efficacy and safety of DOACs remain uncertain in patients with end-stage kidney disease or cirrhosis.

Management of Bleeding from Anticoagulants For life-threatening or intracranial hemorrhage due to heparin or LMWH, administer protamine sulfate. The dabigatran antibody, idarucizumab, is an effective, rapidly acting antidote for dabigatran. Andexanet alfa or protein complex concentrate reverses major bleeding caused by anti-Xa DOACs, but beware of rebound thrombosis. With minor

TABLE 290-5 Take-Home Points from the European Society of Cardiology 2019 Pulmonary Embolism Guidelines

1. Terminology such as “provoked” versus “unprovoked” PE/DVT is no longer supported by the guidelines, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation.
2. Extended oral anticoagulation without an end date should be considered for patients with a first episode of PE and:
 - a. No identifiable risk factor
 - b. A persistent risk factor
 - c. A minor transient or reversible risk factor

Abbreviations: DVT, deep-venous thrombosis; PE, pulmonary embolism.

bleeding, fresh-frozen plasma, vitamin K, or observation without pharmacologic intervention can be considered.

Cancer and Venous Thromboembolism For patients with cancer and VTE, prescribe LMWH as monotherapy or a DOAC in the absence of a gastrointestinal cancer, and continue extended-duration anticoagulation until the patient is declared cancer-free. The National Comprehensive Cancer Network guidelines endorse treatment of VTE with apixaban or edoxaban.

Duration of Anticoagulation Data-driven guidelines from the European Society of Cardiology are changing our conceptual approach to determining the optimal duration of anticoagulation (Tables 290-5 and 290-6). We should no longer classify VTE as “provoked” or “unprovoked,” given that many types of provoked VTE have a similar recurrence rate to unprovoked VTE once anticoagulation is discontinued. Enduring risk factors such as heart failure, chronic lung disease, and inflammatory bowel diseases can heighten the risk of recurrence.

INFERIOR VENA CAVA FILTERS

The two principal indications for insertion of an inferior vena cava filter are (1) active bleeding that precludes anticoagulation and (2) recurrent venous thrombosis despite intensive anticoagulation. Prevention of PE in patients who are not candidates for anticoagulation is a much “softer” indication for filter placement. The filter itself may fail by permitting the passage of small- to medium-size clots via collateral veins that develop. Paradoxically, by providing a nidus for clot formation, filters may increase the DVT rate even though they usually prevent PE. In most situations, place a retrievable rather than a permanent filter.

MANAGEMENT OF MASSIVE PE

For patients with massive PE and hypotension, replete volume with 500 mL of normal saline. Excessive fluid administration exacerbates RV wall stress, causes more profound RV ischemia, and worsens LV compliance and filling by causing further interventricular septal shift toward the LV. Norepinephrine and dobutamine are first-line vasopressor and inotropic agents, respectively, for treatment of PE-related shock. Norepinephrine increases systemic arterial pressure. Dobutamine increases RV inotropy and lowers filling pressures. If

TABLE 290-6 Risk of Recurrent Venous Thromboembolism After Discontinuing Anticoagulation (European Society of Cardiology 2019 Pulmonary Embolism Guidelines)

RISK OF RECURRENCE	EXAMPLES
Low risk (<3% per year)	Major surgery or trauma
Intermediate risk (3–8% per year)	Minor surgery Hospitalized with acute medical illness Pregnancy/estrogens Long-haul flight Inflammatory bowel disease Autoimmune disease No identifiable risk factor (formerly called “unprovoked”)
High risk (>8% per year)	Active cancer Antiphospholipid syndrome

additional hemodynamic circulatory support is required, available, and within the scope of the patient’s goals of care, consider veno-arterial extracorporeal membrane oxygenation (ECMO).

FIBRINOLYSIS

Successful fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE by (1) dissolving much of the anatomically obstructing pulmonary arterial thrombus, (2) preventing the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension, and (3) lysing much of the source of the thrombus in the pelvic or deep leg veins, thereby potentially decreasing the likelihood of recurrent PE.

For massive PE, the U.S. Food and Drug Administration has approved systemically administered 100 mg of recombinant tissue plasminogen activator (tPA) (alteplase) prescribed as a continuous intravenous infusion over 2 h. The sooner thrombolysis is administered, the more effective it is. However, systemic fibrinolysis can be utilized effectively for at least 14 days after the PE has occurred. A popular but controversial off-label dosing regimen is 50 mg of tPA administered over 2 h. This lower dose appears less effective than full-dose tPA but may be associated with fewer bleeding complications.

Contraindications to fibrinolysis include intracranial disease, recent surgery, and trauma. The overall major bleeding rate is ~10%, including a 2–3% risk of intracranial hemorrhage. Careful screening of patients for contraindications to fibrinolytic therapy (Chap. 286) is the best way to minimize bleeding risk.

For patients with submassive PE who have preserved systolic blood pressure but moderate or severe RV dysfunction, use of fibrinolysis remains controversial. A 2019 American Heart Association Scientific Statement suggests consideration of thrombolysis or embolectomy in patients with a lack of clinical improvement, clinical deterioration, clot in transit, severe or persistent RV strain, or signs of low cardiac output.

CATHETER-DIRECTED THERAPY

There are three types of catheter-directed therapy to treat VTE: (1) pharmacologic only, (2) mechanical only, or (3) pharmacomechanical. *Pharmacologic therapy* usually utilizes a low-dose continuous infusion of tPA. *Mechanical therapy* serves as a percutaneous thrombectomy. The procedure usually employs suction, snaring, and extraction of thrombus without using thrombolytic therapy. One mechanical device is a catheter with expandable nitinol disks that traps the thrombus, which is then removed. *Pharmacomechanical therapy* is epitomized by low-energy ultrasound-facilitated low-dose thrombolysis. The low-dose thrombolysis strategy most likely explains the lower major bleeding complication rate compared with systemically administered fibrinolysis.

SURGICAL PULMONARY EMBOLECTOMY

The substantial risk of major hemorrhage with systemically administered fibrinolysis reawakened interest in alternative treatment with surgical embolectomy, an operation that had almost become extinct. More rapid referral for surgery before the onset of irreversible multisystem organ failure, improved surgical technique, and utilization of ECMO have increased the survival rate of surgical pulmonary embolectomy and have markedly improved right ventricular function.

PULMONARY THROMBOENDARTERECTOMY

CTEPH develops in about 2% of acute PE patients. Therefore, PE patients who have initial pulmonary hypertension (often detected initially during echocardiography) should be followed up at about 6 weeks and, if necessary, at 6 months, with repeat echocardiograms to determine whether pulmonary arterial pressure has worsened, plateaued, or abated. Patients impaired by dyspnea due to CTEPH should be considered for pulmonary thromboendarterectomy, which can markedly reduce, and sometimes even cure, pulmonary hypertension (Chap. 294). The operation requires

TABLE 290-7 Prevention of Venous Thromboembolism Among Hospitalized Patients

CONDITION	PROPHYLAXIS STRATEGY
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SC bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Medical oncology (ambulatory)	Apixaban or rivaroxaban for up to 6 months in high-risk patients with cancer starting a new chemotherapy regimen
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Aspirin 81 mg twice daily Rivaroxaban 10 mg daily, beginning 6–10 h postoperatively Dabigatran 110 mg first day, then 220 mg daily Apixaban 2.5 mg bid, beginning 12–24 h postoperatively Warfarin (target INR 2.0) Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Medically ill patients, especially if immobilized, with a history of prior VTE, with an indwelling central venous catheter, or with cancer (but without active gastroduodenal ulcer, major bleeding within 3 months, or platelet count <50,000)	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Medically ill patients about to be discharged from hospital	Rivaroxaban 10 mg daily for about 5 weeks (rarely prescribed for this indication)
Anticoagulation contraindicated	Intermittent pneumatic compression devices and/or graduated vascular below-knee compression stockings

Abbreviations: INR, international normalized ratio; VTE, venous thromboembolism.

median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of hypothermic circulatory arrest. The mortality rate at experienced centers is 1–5%. Inoperable patients should be managed with pulmonary vasodilator therapy and balloon angioplasty of pulmonary arterial webs.

PREVENTION OF VTE

Prevention of DVT and PE (Table 290-7) is of paramount importance because VTE is difficult to detect and poses a profound medical and economic burden. Low-dose UFH or LMWH is the most common form of in-hospital prophylaxis. Computerized reminder systems in ambulatory and in-hospital practices can increase the use of preventive measures and, at Brigham and Women’s Hospital, have reduced the symptomatic VTE rate.

EMOTIONAL SUPPORT

Patients with VTE may feel overwhelmed when they learn that they are suffering from PE or DVT. Some have never previously encountered serious cardiovascular illness. They often assume they will have a reduced life expectancy. They worry about the health of their families and the genetic implications of their illness. At Brigham and Women’s Hospital, a physician-nurse-facilitated PE support group was initiated to address these concerns and has met monthly for >30 years. The non-profit North American Thrombosis Forum (www.thrombosis.org) runs monthly online support groups that garner worldwide participation.

FURTHER READING

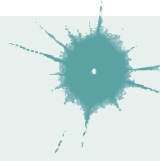
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291

Diseases of the Aorta

Mark A. Creager, Joseph Loscalzo



The aorta is the conduit through which blood ejected from the left ventricle is delivered to the systemic arterial bed. In adults, its diameter is ~3.5 cm at the origin and in the ascending portion, ~2.5 cm in the descending portion in the thorax, and 1.8–2.0 cm in the abdomen. The aortic wall consists of a thin intima composed of endothelium, subendothelial connective tissue, and an internal elastic lamina; a thick tunica media composed of smooth muscle cells, elastic fibers, collagen, and extracellular matrix; and an adventitia composed primarily of connective tissue enclosing the vasa vasorum and nervi vasculares. In addition to the conduit function of the aorta, its viscoelastic and compliant properties serve a buffering function. The aorta is distended during systole to allow a portion of the stroke volume and elastic energy to be stored, and it recoils during diastole so that blood continues to flow to the periphery. Owing to its continuous exposure to high pulsatile pressure and shear stress, the aorta is particularly prone to injury and disease resulting from mechanical trauma. The aorta is also more prone to rupture than is any other vessel, especially with the development of aneurysmal dilation, since its wall tension, as governed by Laplace's law (i.e., proportional to the product of pressure and radius), will be increased.

CONGENITAL ANOMALIES OF THE AORTA

Congenital anomalies of the aorta usually involve the aortic arch and its branches. Symptoms such as dysphagia, stridor, and cough may occur if an anomaly causes a ring around or otherwise compresses the esophagus or trachea. Anomalies associated with symptoms include double aortic arch, origin of the right subclavian artery distal to the left subclavian artery, and right-sided aortic arch with an aberrant left subclavian artery. A Kommerell diverticulum

is an anatomic remnant of a right aortic arch. Most congenital anomalies of the aorta do not cause symptoms and are detected during catheter-based procedures. The diagnosis of suspected congenital anomalies of the aorta typically is confirmed by computed tomographic (CT) or magnetic resonance (MR) angiography. Surgery is used to treat symptomatic anomalies.

Coarctation of the aorta (**Chap. 280**) typically occurs near the insertion of the ligamentum arteriosum, adjacent to the left subclavian artery. It may be associated with a bicuspid aortic valve, aortic arch hypoplasia, other congenital heart defects, and intracranial aneurysms. A pulse delay or pressure differential between the upper and lower extremities should raise suspicion of aortic coarctation. Imaging modalities, including echocardiography, CT, and MR angiography are used to confirm the diagnosis. If untreated, hypertension develops in the arteries proximal to the coarctation. Treatment of hemodynamically significant aortic coarctation includes endovascular stent implantation if feasible or surgical repair.

AORTIC ANEURYSM

An *aneurysm* is defined as a pathologic dilation of a segment of a blood vessel. A *true aneurysm* involves all three layers of the vessel wall and is distinguished from a *pseudoaneurysm*, in which the intimal and medial layers are disrupted and the dilated segment of the aorta is lined by adventitia only and, at times, by perivascular clot. Aneurysms also may be classified according to their gross appearance. A *fusiform aneurysm* affects the entire circumference of a segment of the vessel, resulting in a diffusely dilated artery. In contrast, a *saccular aneurysm* involves only a portion of the circumference, resulting in an outpouching of the vessel wall. Aortic aneurysms also are classified according to location, i.e., abdominal versus thoracic. Aneurysms of the descending thoracic aorta are usually contiguous with infradiaphragmatic aneurysms and are referred to as *thoracoabdominal aortic aneurysms*.

ETIOLOGY

Aortic aneurysms result from conditions that cause degradation or abnormal production of the structural components of the aortic wall: elastin and collagen. The causes of aortic aneurysms may be broadly categorized as degenerative or sporadic, heritable, congenital, aortitis, infective, and trauma (**Table 291-1**). Inflammation, oxidative stress, proteolysis, and biomechanical wall stress contribute to the degenerative processes that characterize most aneurysms of the abdominal and descending thoracic aorta. These are mediated by B-cell and T-cell lymphocytes, macrophages, inflammatory cytokines, and matrix metalloproteinases that degrade elastin and collagen and alter the tensile strength and ability of the aorta to accommodate pulsatile stretch. The associated histopathology demonstrates destruction of elastin and collagen, decreased vascular smooth muscle, in-growth of new blood vessels, and inflammation. Factors associated with degenerative aortic aneurysms include aging, cigarette smoking, hypercholesterolemia, hypertension, and male sex.

The most common pathologic condition associated with degenerative aortic aneurysms is *atherosclerosis*. Many patients with aortic aneurysms have coexisting risk factors for atherosclerosis, as well as atherosclerosis in other blood vessels.

The pathologic condition of aortic aneurysms associated with genetic or developmental diseases is medial degeneration, a histopathologic term used to describe the degeneration of collagen and elastic fibers in the tunica media of the aorta as well as the loss of medial cells that are replaced by multiple clefts of mucoid material, such as proteoglycans. Medial degeneration characteristically affects the proximal aorta, results in circumferential weakness and dilation, and leads to the development of fusiform aneurysms involving the ascending aorta and the sinuses of Valsalva. It is found in patients with Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome (**Chap. 425**), hypertension, bicuspid aortic valves, Turner syndrome, and familial thoracic aortic aneurysm syndromes. It sometimes appears as an isolated condition in patients without any other apparent disease. Thoracic and abdominal aortic aneurysms also occur in patients with fibromuscular dysplasia, although the nature of the aortic pathology is not established.

TABLE 291-1 Diseases of the Aorta: Etiology and Associated Factors

Aortic aneurysm
Degenerative/sporadic
Aging
Cigarette smoking
Hypercholesterolemia
Hypertension
Atherosclerosis
Heritable
Marfan syndrome
Loeys-Dietz syndrome
Ehlers-Danlos syndrome type IV
Aneurysm-osteoarthritis syndrome
Smooth muscle dysfunction syndrome
Familial (nonsyndromic)
Congenital
Bicuspid aortic valve
Turner syndrome
Aortic coarctation
Fibromuscular dysplasia
Chronic aortic dissection
Aortitis (see below)
Infective (see below)
Trauma
Acute aortic syndromes (aortic dissection, acute intramural hematoma, penetrating atherosclerotic ulcer)
Degenerative disorders (see above)
Heritable/disorders (see above)
Congenital disorders (see above)
Hypertension
Aortitis (see below)
Pregnancy
Trauma
Aortic occlusion
Atherosclerosis
Thromboembolism
Aortitis
Vasculitis
Takayasu's arteritis
Giant cell arteritis
IgG4-related aortitis
Isolated aortitis
Rheumatic
Rheumatoid aortitis
HLA-B27-associated spondyloarthropathies
Behçet syndrome
Cogan syndrome
Infective
Syphilis
Tuberculosis
Mycotic (<i>Salmonella</i> , staphylococcal, streptococcal, fungal)

Familial clusterings of aortic aneurysms occur in 20% of patients, suggesting a hereditary basis for the disease. Mutations of the gene that encodes fibrillin-1 are present in patients with Marfan syndrome. Fibrillin-1 is an important component of extracellular microfibrils, which support the architecture of elastic fibers and other connective tissue. Deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by transforming growth factor β (TGF- β). Loeys-Dietz syndrome is caused by mutations in the genes that encode

TGF- β isoforms (*TGFB2* and *TGFB3*), TGF- β receptors 1 (*TGFB1*) and 2 (*TGFB2*), and *SMAD3*, which encodes a downstream signaling protein involved with TGF binding to its receptors. Increased signaling by TGF- β and mutations of *TGFB1*, *TGFB2*, as well as *TGFB2* and *TGFB3*, may cause thoracic aortic aneurysms. Thoracic aortic aneurysm is associated with autosomal dominant polycystic kidney disease, which is caused by mutations in *PKD1*. Mutations of the genes encoding the smooth muscle-specific alpha-actin (*ACTA2*), smooth muscle cell-specific myosin heavy chain 11 (*MYH11*), myosin light chain kinase (*MYLK*), and type I cGMP-dependent protein kinase (*PRKG1*), as well as mutations of *TGFB2* and *SMAD3* and several other pathogenic variants, have been reported in some patients with nonsyndromic familial thoracic aortic aneurysms. Mutations in type III procollagen (*COL3A1*) have been implicated in vascular Ehlers-Danlos syndrome.

The infectious causes of aortic aneurysms include syphilis, tuberculosis, and other bacterial infections. *Syphilis* (Chap. 187) is a relatively uncommon cause of aortic aneurysm. Syphilitic periaortitis and meso-aortitis damage elastic fibers, resulting in thickening and weakening of the aortic wall. Approximately 90% of syphilitic aneurysms are located in the ascending aorta or aortic arch. *Tuberculous aneurysms* (Chap. 183) typically affect the thoracic aorta and result from direct extension of infection from hilar lymph nodes or contiguous abscesses as well as from bacterial seeding. Loss of aortic wall elasticity results from granulomatous destruction of the medial layer. A *mycotic aneurysm* is a rare condition that develops as a result of staphylococcal, streptococcal, *Salmonella*, or other bacterial or fungal infections of the aorta, usually at an atherosclerotic plaque. These aneurysms are usually saccular. Blood cultures are often positive and reveal the nature of the infective agent.

Vasculitides associated with aortic aneurysm include Takayasu arteritis and giant cell arteritis, which may cause aneurysms of the aortic arch and descending thoracic aorta. Thoracic and abdominal aortic aneurysms also occur in patients with IgG4-related systemic disease or those with isolated aortitis. Spondyloarthropathies such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, relapsing polychondritis, and reactive arthritis are associated with dilation of the ascending aorta. Aortic aneurysms also occur in patients with Behçet syndrome (Chap. 376) and Cogan syndrome. *Traumatic aneurysms* may occur after penetrating or nonpenetrating chest trauma and most commonly affect the descending thoracic aorta just beyond the site of insertion of the ligamentum arteriosum. Chronic aortic dissections are associated with weakening of the aortic wall that may lead to the development of aneurysmal dilatation.

■ THORACIC AORTIC ANEURYSMS

A contemporary definition of an aneurysm affecting the aortic root and ascending aorta is that of the diameter ≥ 4.5 cm, whereas a diameter of 4.0 cm to 4.4 cm is defined as aortic dilation. An aneurysm of the descending thoracic aorta and abdominal aorta is designated when their diameters are dilated 50% more than the adjacent normal diameter. The clinical manifestations and natural history of thoracic aortic aneurysms depend on their cause and location. Medial degeneration is the most common pathology associated with ascending aortic aneurysms, whereas atherosclerosis is the condition most frequently associated with aneurysms of the descending thoracic aorta. The average growth rate of thoracic aortic aneurysms is 0.1–0.2 cm per year. The risk of rupture is related to the size of the aneurysm and the presence of symptoms, ranging approximately from 2–3% per year for thoracic aortic aneurysms <4.0 cm in diameter to 7% per year for those >6 cm in diameter. Thoracic aortic aneurysms associated with Marfan syndrome may expand at a greater rate. Some patients with Loeys-Dietz syndrome, such as those with the *TGFB1* and *TGFB2* pathogenic variants and some with nonsyndromic familial thoracic aortic disease, are at greater risk of rupture at smaller aortic root sizes than those with Marfan syndrome. Most thoracic aortic aneurysms are asymptomatic; however, compression or erosion of adjacent tissue by aneurysms may cause symptoms such as chest pain, shortness of breath, cough, hoarseness, and dysphagia. Aneurysmal dilation of the ascending aorta may cause congestive heart failure as a consequence of aortic regurgitation,



FIGURE 291-1 A chest x-ray of a patient with a thoracic aortic aneurysm.

and compression of the superior vena cava may produce congestion of the head, neck, and upper extremities.

A chest x-ray may be the first test that suggests the diagnosis of a thoracic aortic aneurysm (**Fig. 291-1**). Findings include widening of the mediastinal shadow and displacement or compression of the trachea or left main stem bronchus. Echocardiography, particularly transesophageal echocardiography, can be used to assess the proximal ascending aorta and descending thoracic aorta. Contrast-enhanced CT, magnetic resonance imaging (MRI), and conventional invasive aortography are sensitive and specific tests for assessment of aneurysms of the thoracic aorta and involvement of branch vessels (**Fig. 291-2**). In asymptomatic patients whose aneurysms are too small to justify surgery, noninvasive testing with either contrast-enhanced CT or MRI should be performed initially at least every 6–12 months to monitor expansion. Subsequent surveillance imaging should be performed every 6–24 months depending on the size, stability of prior measurements, and the underlying cause.

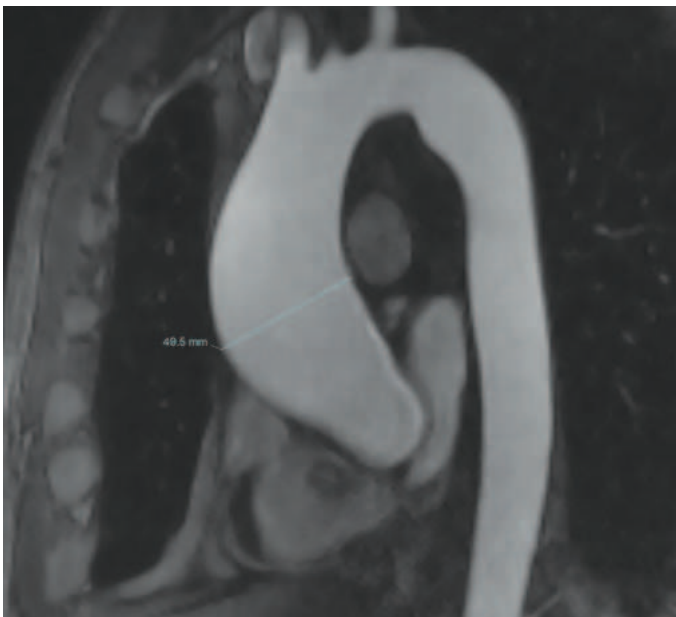


FIGURE 291-2 A magnetic resonance angiogram demonstrating a fusiform aneurysm of the ascending thoracic aorta. (Courtesy of Dr. Michael Steigner, Brigham and Women's Hospital, Boston, MA, with permission.)

Genetic testing is recommended in patients with ascending thoracic aortic disease who have features of Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome, or who present when they are <60 years of age.

TREATMENT

Thoracic Aortic Aneurysms

Many of the treatment recommendations herein are derived from the recent American Heart Association (AHA)/American College of Cardiology (ACC) Aortic Disease Clinical Practice Guidelines. Treatment with either a β -adrenergic blocker or angiotensin receptor antagonist currently is recommended for patients with thoracic aortic aneurysms associated with Marfan syndrome and Loeys-Dietz syndrome who have evidence of aortic root dilatation to reduce the rate of further expansion. Clinical outcome trials have found that the rate of aortic root enlargement in patients with Marfan syndrome was similar with a β -adrenergic blocker, such as atenolol, and an angiotensin receptor antagonist, such as losartan. These classes of drugs likely confer beneficial effects by different mechanisms. β -adrenergic blockers may decrease the rate of aortic dilation in these patients by reducing stiffness, and angiotensin receptor antagonists may reduce the rate of aortic dilation by blocking TGF- β signaling. Combination therapy with both a β -adrenergic blocker and angiotensin receptor antagonist may be considered. In patients with Ehlers-Danlos syndrome, celiprolol, a β -adrenergic blocker with vasodilator properties, has shown efficacy, but is not available in the United States. For these and other patients with thoracic aortic aneurysms, additional medical therapy should be given as necessary to control hypertension. Risk factor modification with lipid-lowering therapy, smoking cessation interventions, as well as low-dose aspirin, is advised for patients with degenerative thoracic aortic aneurysms associated with atherosclerosis. Operative repair with placement of a prosthetic graft is indicated in patients with symptomatic ascending thoracic aortic aneurysms, and for most asymptomatic aneurysms, including those associated with bicuspid aortic valves, when the aortic root or ascending aortic diameter is ≥ 5.0 to ≥ 5.5 cm. The lower threshold applies to patients with high-risk features, such as a family history of aortic dissection or an aortic growth rate ≥ 0.3 cm per year for 2 years or when the growth rate is >0.5 cm per year, and when performed under the direction of an experienced multidisciplinary aortic team. Replacement of the ascending aorta ≥ 4.5 cm is reasonable in patients with bicuspid aortic valves undergoing aortic valve replacement because of severe aortic stenosis or aortic regurgitation. In patients with Marfan syndrome, aortic root and ascending thoracic aortic aneurysms of ≥ 4.5 to ≥ 5.0 cm should be considered for surgery, with the threshold also depending on the presence of high-risk features. Due to the higher risk of dissection at smaller aortic sizes in patients with Loeys-Dietz syndrome and those with nonsyndromic familial thoracic aortic aneurysms, the aortic diameter threshold for operative repair ranges from ≥ 4.0 to ≥ 5.0 cm, depending on the genetic variant and presence of high-risk features. Repair is indicated for patients with isolated aortic arch aneurysms and descending thoracic aortic aneurysms when the diameter is ≥ 5.5 cm. The threshold for repair of a descending thoracic aortic aneurysm of ≥ 5.0 cm may be considered in patients with syndromic and nonsyndromic heritable aortopathies or when the diameter of a descending thoracic aortic aneurysm has increased >0.5 cm per year.

ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms occur more frequently in males than in females, and the incidence increases with age. Cigarette smoking is a potent modifiable risk factor. Abdominal aortic aneurysms ≥ 4.0 cm may affect 1–2% of men aged >50 years. At least 90% of all abdominal aortic aneurysms >4.0 cm are related to atherosclerotic disease, and most of these aneurysms are below the level of the renal arteries.



A



B

FIGURE 291-3 A computed tomographic angiogram depicting a fusiform abdominal aortic aneurysm before (A) and after (B) treatment with a bifurcated stent graft. (Courtesy of Drs. Elizabeth George and Frank Rybicki, Brigham and Women's Hospital, Boston, MA, with permission.)

Prognosis is related to both the size of the aneurysm and the severity of coexisting coronary artery and cerebrovascular disease. The risk of rupture increases with the size of the aneurysm: the 5-year risk for aneurysms <5 cm is 1–2%, whereas it is 20–40% for aneurysms >5 cm in diameter. The formation of mural thrombi within aneurysms may predispose to peripheral embolization.

An abdominal aortic aneurysm commonly produces no symptoms. It usually is detected on routine examination as a palpable, pulsatile, expansile, and nontender mass, or it is an incidental finding observed on an abdominal imaging study performed for other reasons. As abdominal aortic aneurysms expand, however, they may become painful. Some patients complain of strong pulsations in the abdomen; others experience pain in the chest, lower back, or scrotum. Aneurysmal pain is usually a harbinger of rupture and represents a medical emergency. More often, acute rupture occurs without any prior warning, and this complication is always life-threatening. Rarely, there is leakage of the aneurysm with severe pain and tenderness. Acute pain and hypotension occur with rupture of the aneurysm, which requires an emergency operation or endovascular repair.

Abdominal radiography may demonstrate the calcified outline of the aneurysm; however, ~25% of aneurysms are not calcified and cannot be visualized by x-ray imaging. An abdominal ultrasound can delineate the transverse and longitudinal dimensions of an abdominal aortic aneurysm and may detect mural thrombus. Abdominal ultrasound is useful for serial documentation of aneurysm size and can be used to screen patients at risk for developing an aortic aneurysm. In a large study, ultrasound screening of men aged 65–74 years was associated with a risk reduction in aneurysm-related death of 42%. In a meta-analysis of population-based randomized clinical trials, ultrasound screening of men aged 65 years or older was associated with a 35% risk reduction in aneurysm-related death over 12–15 years. According to the AHA/ACC Guidelines on Aortic Disease, screening by ultrasonography is recommended for men aged ≥65 years who have ever smoked. Although the prevalence of abdominal aortic aneurysms is less in women than in men, the risk of abdominal aortic aneurysms is still substantially increased in women who have smoked. Accordingly, it is reasonable to consider abdominal aortic aneurysm screening in women aged ≥65 years who have ever smoked. In addition, screening for abdominal aortic aneurysms is recommended for males and

females ≥65 years who have siblings or offspring with abdominal aortic aneurysms. Individuals with thoracic aortic or peripheral arterial aneurysms should also undergo screening for abdominal aortic aneurysms. CT with contrast and MRI are accurate noninvasive tests to determine the location and size of abdominal aortic aneurysms and to plan endovascular or open surgical repair (Fig. 291-3A). Contrast aortography may be used for the evaluation of patients with aneurysms, but the procedure carries a small risk of complications such as bleeding, allergic reactions, and atheroembolism. Since the presence of mural thrombi may reduce the luminal size, aortography may underestimate the diameter of an aneurysm.

TREATMENT

Abdominal Aortic Aneurysms

Many of the treatment recommendations for abdominal aortic aneurysms are derived from the AHA/ACC Aortic Disease Practice Guidelines. Statins are indicated to reduce the risk of cardiovascular events related to atherosclerosis. Medical therapies, such as β -adrenergic blockers and renin-angiotensin inhibitors, have not proven effective in reducing the rate of aneurysm growth. Nonetheless, antihypertensive therapy to lower the blood pressure to <130/<80 mmHg is recommended to reduce the risk of adverse cardiovascular events. Similarly, antiplatelet agents, such as aspirin, are recommended in patients with abdominal aortic aneurysms to reduce the risk of adverse cardiovascular outcomes, but their effects on abdominal aortic aneurysm-specific outcomes are not established. Operative repair of the aneurysm with insertion of a prosthetic graft or endovascular placement of an aortic stent graft (Fig. 291-3B) is indicated for abdominal aortic aneurysms of any size that are expanding rapidly or are associated with symptoms. For asymptomatic aneurysms, abdominal aortic aneurysm repair is indicated if the diameter is ≥5.5 cm in men and ≥5.0 cm in women. In randomized trials of patients with abdominal aortic aneurysms <5.5 cm, there was no difference in the long-term (>8-year) mortality rate between those followed with ultrasound surveillance and those undergoing elective endovascular or surgical repair. The risk of rupture, however, was higher in women than in men at smaller diameters. Thus, serial noninvasive follow-up of smaller aneurysms

(<5.5 cm in men and <5.0 cm in women) is an alternative to immediate repair. The decision to perform an open surgical operation or endovascular repair is based in part on the vascular anatomy and comorbid conditions. Endovascular repair of abdominal aortic aneurysms has a lower short-term morbidity rate but a comparable long-term mortality rate with open surgical reconstruction. Long-term surveillance with CT or MR aortography is indicated after endovascular repair to detect leaks and possible aneurysm expansion.

In surgical candidates, careful preoperative cardiac and general medical evaluations (followed by appropriate therapy for complicating conditions) are essential. Preexisting coronary artery disease, congestive heart failure, pulmonary disease, diabetes mellitus, and advanced age add to the risk of surgery. With careful preoperative cardiac evaluation and postoperative care, the operative mortality rate approximates 1–2%. After acute rupture, the mortality rate of emergent operation is 45–50%. Endovascular repair with stent placement is an alternative approach to treat ruptured aneurysms and may be associated with a lower mortality rate.

ACUTE AORTIC SYNDROMES

The four major acute aortic syndromes are aortic rupture (discussed earlier), aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer. Aortic dissection is caused by a tear of the intima. It often occurs along the right lateral wall of the ascending aorta where the hydraulic shear stress is high. Another common site is the descending thoracic aorta just below the ligamentum arteriosum. The initiating event is either a primary intimal tear with secondary dissection into the media or a medial hemorrhage that dissects into and disrupts the intima. The pulsatile aortic flow then dissects along the elastic lamellar plates of the aorta and creates a false lumen. The dissection usually propagates distally down the descending aorta and into its major branches, but it may propagate proximally. Distal propagation may be limited by atherosclerotic plaque. In some cases, a secondary distal intimal disruption occurs, resulting in the reentry of blood from the false to the true lumen.

There are at least two important pathologic and radiologic variants of aortic dissection: intramural hematoma without an intimal flap and penetrating atherosclerotic ulcer. Acute intramural hematoma is thought to result from rupture of the vasa vasorum with hemorrhage into the wall of the aorta. Most of these hematomas occur in the descending thoracic aorta. Acute intramural hematomas may progress to dissection and rupture. Penetrating atherosclerotic ulcers are caused by erosion of a plaque into the aortic media, are usually localized, but may evolve into an intramural hematoma and also progress to dissection and rupture. They are found primarily in the middle and distal portions of the descending thoracic aorta and are associated with extensive atherosclerotic disease. The ulcer can erode beyond the internal elastic lamina, leading to medial hematoma, and may progress to false aneurysm formation or rupture.

Several classification schemes have been developed for thoracic aortic dissections. DeBakey and colleagues initially classified aortic dissections as type I, in which an intimal tear occurs in the ascending aorta but the dissection may propagate to the aortic arch, the descending thoracic aorta, and even the abdominal aorta; type II, in which the dissection is limited to the ascending aorta; and type III, in which the intimal tear is located in the descending aorta with distal propagation of the dissection (Fig. 291-4). Another classification (Stanford) is that of type A, in which the dissection involves the ascending aorta (proximal dissection), and type B, in which it is limited to the arch and/or descending aorta (distal dissection). From a management standpoint, classification of aortic dissections and intramural hematomas into type A or B is more practical and useful, since DeBakey types I and II are managed in a similar manner.

The factors that predispose to aortic dissection include those associated with medial degeneration and others that increase aortic wall stress (Table 291-1). Systemic hypertension is a coexisting condition in 70% of patients. Aortic dissection is the major cause of morbidity and

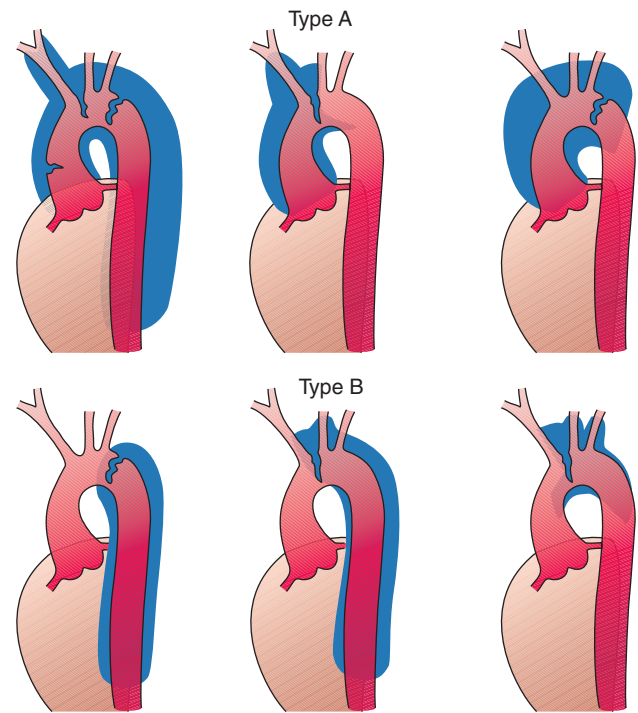


FIGURE 291-4 Classification of aortic dissections. Stanford classification: Type A dissections (top) involve the ascending aorta independent of site of tear and distal extension; type B dissections (bottom) involve transverse and/or descending aorta without involvement of the ascending aorta. DeBakey classification: Type I dissection involves ascending to descending aorta (top left); type II dissection is limited to ascending or transverse aorta, without descending aorta (top center + top right); type III dissection involves descending aorta only (bottom left). (Reproduced with permission from DC Miller, in RM Doroghazi, EE Slater [eds]: *Aortic Dissection*. New York, McGraw-Hill, 1983.)

mortality in patients with Marfan syndrome (Chap. 425) or Loeys-Dietz syndrome, and similarly may affect patients with Ehlers-Danlos syndrome. The incidence also is increased in patients with inflammatory aortitis (i.e., Takayasu's arteritis, giant cell arteritis), congenital aortic valve anomalies (e.g., bicuspid valve), coarctation of the aorta, and a history of aortic trauma. In addition, the risk of dissection is increased in otherwise normal women during the third trimester of pregnancy. Aortic dissection also may occur as a consequence of weightlifting, cocaine use, or deceleration injury.

CLINICAL MANIFESTATIONS

The peak incidence of aortic dissection is in the sixth and seventh decades. Men are more affected than women by a ratio of 2:1. The presentations of aortic dissection and its variants are the consequences of intimal tear, dissecting hematoma, occlusion of involved arteries, and compression of adjacent tissues. Acute aortic dissection presents with the sudden onset of pain (Chap. 15), which often is described as very severe and tearing and is associated with diaphoresis. The pain may be localized to the front or back of the chest, often the interscapular region, and typically migrates with propagation of the dissection. Other symptoms include syncope, dyspnea, and weakness. Physical findings may include hypertension or hypotension, loss of pulses, aortic regurgitation, pulmonary edema, and neurologic findings due to carotid artery obstruction (hemiplegia, hemianesthesia) or spinal cord ischemia (paraplegia). Bowel ischemia, hematuria, and myocardial ischemia all may occur. These clinical manifestations reflect complications resulting from the dissection occluding the major arteries. Furthermore, clinical manifestations may result from the compression of adjacent structures (e.g., superior cervical ganglia, superior vena cava, bronchus, esophagus) by the expanding dissection causing aneurysmal dilation and include Horner's syndrome, superior vena cava syndrome, hoarseness, dysphagia, and airway compromise. Hemopericardium and cardiac tamponade may complicate a type A lesion with retrograde dissection. Acute aortic regurgitation is an important and common (>50%) complication of proximal dissection. It is the outcome of either

a circumferential tear that widens the aortic root or a disruption of the annulus by a dissecting hematoma that tears a leaflet(s) or displaces it inferior to the line of closure. Signs of aortic regurgitation include bounding pulses, a wide pulse pressure, a diastolic murmur often radiating along the right sternal border, and evidence of congestive heart failure. The clinical manifestations depend on the severity of the regurgitation.

In dissections involving the ascending aorta, the chest x-ray often reveals a widened superior mediastinum. A pleural effusion (usually left-sided) also may be present. This effusion is typically serosanguineous and not indicative of rupture unless accompanied by hypotension and falling hematocrit. In dissections of the descending thoracic aorta, a widened mediastinum may be observed on chest x-ray. In addition, the descending aorta may appear to be wider than the ascending portion. An electrocardiogram that shows no evidence of myocardial ischemia is helpful in distinguishing aortic dissection from myocardial infarction among patients who present with chest pain. Rarely, the dissection involves the right or, less commonly, left coronary ostium and causes acute myocardial infarction.

The diagnosis of aortic dissection can be established by noninvasive techniques such as echocardiography, CT, and MRI. Aortography is used less commonly because of the accuracy of these noninvasive techniques. Transthoracic echocardiography can be performed simply and rapidly and has an overall sensitivity of 60–85% for aortic dissection. For diagnosing proximal ascending aortic dissections, its sensitivity exceeds 80%; it is less useful for detecting dissection of the arch and descending thoracic aorta. Transesophageal echocardiography requires greater skill and patient cooperation but is very accurate in identifying dissections of the ascending and descending thoracic aorta but not the arch, achieving 98% sensitivity and ~90% specificity. Echocardiography also provides important information regarding the presence and severity of aortic regurgitation and pericardial effusion. CT and MRI are both highly accurate in identifying the intimal flap and the extent of the dissection and involvement of major arteries; each has a sensitivity and specificity >90%. They are useful in recognizing intramural hemorrhage and penetrating ulcers. The relative utility of CT, MRI, and transesophageal echocardiography depends on the availability and expertise in individual institutions, although among these, CT is the imaging method most often used due to the presence of CT scanners near emergency rooms and the rapidity of performance.

TREATMENT

Aortic Dissection

Medical therapy should be initiated as soon as the diagnosis is considered. The patient should be admitted to an intensive care unit for hemodynamic monitoring. Unless hypotension is present, therapy should be aimed at reducing cardiac contractility and systemic arterial pressure, and thus shear stress. For acute dissection, unless contraindicated, β -adrenergic blockers should be administered parenterally, using intravenous propranolol, metoprolol, or the short-acting esmolol to achieve a heart rate of 60–80 beats/min. This should be accompanied by intravenous dilators, such as sodium nitroprusside, if needed to lower systolic blood pressure to ≤ 120 mmHg. Labetalol (**Chap. 288**), a drug with both β - and α -adrenergic blocking properties, also may be used as a parenteral agent in acute therapy for dissection.

The calcium channel antagonists verapamil and diltiazem may be used intravenously if nitroprusside or β -adrenergic blockers cannot be employed. The addition of a parenteral angiotensin-converting enzyme (ACE) inhibitor such as enalaprilat to a β -adrenergic blocker also may be considered. Isolated use of a direct vasodilator such as hydralazine is contraindicated because these agents can increase hydraulic shear and heart rate and may propagate the dissection.

Emergent or urgent surgical correction is the preferred treatment for acute ascending aortic dissections and intramural hematomas (type A). Surgery involves excision of the intimal flap, obliteration of the false lumen, and placement of an interposition graft. Aortic

valve repair or aortic root replacement with a composite valve-graft conduit is used if the aortic valve is disrupted. The overall in-hospital mortality rate after surgical treatment of patients with aortic dissection is reported to be 15–25%. The major causes of perioperative mortality and morbidity include myocardial infarction, paraplegia, renal failure, tamponade, hemorrhage, and sepsis. Thoracic endovascular aortic repair with an endoluminal stent graft is indicated for complicated type B dissections, including those characterized by propagation, compromise of major aortic branches, impending rupture, or continued pain. Other transcatheter techniques, such as fenestration of the intimal flaps and stenting of narrowed branch vessels to increase flow to compromised organs, are used in selected patients. Surgical correction is indicated for complicated type B dissections, particularly if endovascular repair is not feasible. Hybrid procedures consisting of both surgery and endovascular repair may be used when the dissection involves both the aortic arch and the descending thoracic aorta. For uncomplicated and stable distal dissections and intramural hematomas (type B), medical therapy is the preferred treatment. The in-hospital mortality rate of medically treated patients with type B dissection is ~12%. Long-term therapy for patients with aortic dissection and intramural hematomas (with or without surgery) consists of control of hypertension and reduction of cardiac contractility with the use of β -adrenergic blockers plus other antihypertensive agents, such as ACE inhibitors or calcium antagonists. Patients with chronic type B dissection and intramural hematomas should be followed on an outpatient basis initially at 1 month, 6 months, and 12 months, and then, if stable, every 12 months with contrast-enhanced CT or MRI to detect propagation or expansion. Patients with Marfan syndrome are at high risk for postdissection complications. The long-term prognosis following hospital discharge for patients with treated dissections is generally good with careful follow-up; the 10-year survival rate is ~60%.

■ CHRONIC ATHEROSCLEROTIC OCCLUSIVE DISEASE

Atherosclerosis may affect the thoracic and abdominal aorta. Occlusive aortic disease caused by atherosclerosis usually is confined to the distal abdominal aorta below the renal arteries. Frequently the disease extends to the iliac arteries (**Chap. 292**). Claudication characteristically involves the buttocks, thighs, and calves and may be associated with impotence in males (Leriche syndrome). The severity of the symptoms depends on the adequacy of collaterals. With sufficient collateral blood flow, a complete occlusion of the abdominal aorta may occur without the development of ischemic symptoms. The physical findings include the absence of femoral and other distal pulses bilaterally and the detection of an audible bruit over the abdomen (usually at or below the umbilicus) and the common femoral arteries. Atrophic skin, loss of hair, and coolness of the lower extremities usually are observed. In advanced ischemia, rubor on dependency and pallor on elevation can be seen.

The diagnosis usually is established by physical examination and noninvasive testing, including leg pressure measurements, Doppler velocity analysis, pulse volume recordings, and duplex ultrasonography. The anatomy may be defined by MRI, CT, or conventional contrast angiography, typically performed when one is considering revascularization. Catheter-based endovascular or operative treatment is indicated in patients with lifestyle-limiting or debilitating symptoms of claudication and patients with chronic limb-threatening ischemia.

■ ACUTE AORTIC OCCLUSION

Acute occlusion in the distal abdominal aorta constitutes a medical emergency because it threatens the viability of the lower extremities; it usually results from an occlusive (saddle) embolus that almost always originates from the heart. Rarely, acute occlusion may occur as the result of in situ thrombosis in a preexisting severely narrowed segment of the aorta.

The clinical picture is one of acute ischemia of the lower extremities. Severe rest pain, coolness, and pallor of the lower extremities and the absence of distal pulses bilaterally are the usual manifestations.

Diagnosis should be established rapidly by MRI, CT, or aortography. Emergency thrombectomy or revascularization is indicated.

AORTITIS

Aortitis, a term referring to inflammatory disease of the aorta, may be caused by large vessel vasculitides such as Takayasu arteritis, giant cell arteritis, IgG4-related systemic disease, isolated aortitis, rheumatic and HLA-B27-associated spondyloarthropathies, Behçet syndrome, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, Cogan syndrome, Erdheim-Chester disease, and infections such as syphilis, tuberculosis, and *Salmonella*, or it may be associated with retroperitoneal fibrosis. Aortitis may result in aneurysmal dilation and aortic regurgitation, occlusion of the aorta and its branch vessels, or acute aortic syndromes.

■ TAKAYASU ARTERITIS

(See also Chap. 375) This inflammatory disease often affects the ascending aorta and aortic arch, causing obstruction of the aorta and its major arteries. Takayasu arteritis is also termed *pulseless disease* because of the frequent occlusion of the large arteries originating from the aorta. It also may involve the descending thoracic and abdominal aorta and occlude large branches such as the renal arteries. Aortic aneurysms also may occur. The pathology is a panarteritis characterized by mononuclear cells and occasionally giant cells, with marked intimal hyperplasia, medial and adventitial thickening, and, in the chronic form, fibrotic occlusion. The disease is most prevalent in young females of Asian descent but does occur in women of other geographic and ethnic origins and also in young men. During the acute stage, fever, malaise, weight loss, and other systemic symptoms may be evident. Elevations of the erythrocyte sedimentation rate and C-reactive protein are common. The chronic stages of the disease, which is intermittently active, present with symptoms related to large artery occlusion, such as upper extremity claudication, cerebral ischemia, and syncope. The process is progressive, and there is no definitive therapy. Glucocorticoids are effective in most patients during the acute phase. Other immunosuppressive agents, such as methotrexate, azathioprine, leflunomide, or mycophenolate, are prescribed to some patients to lower glucocorticoid requirements and treat relapses. Biologically targeted agents, such as the tumor necrosis factor (TNF) inhibitors etanercept and infliximab, are also used, but efficacy has not been established in randomized clinical trials. Surgical bypass or endovascular intervention of a critically stenotic artery may be necessary.

■ GIANT CELL ARTERITIS

(See also Chap. 375) This vasculitis occurs in older individuals and affects women more often than men. Primarily large and medium-size arteries are affected. The pathology is that of focal granulomatous lesions involving the entire arterial wall; it frequently is associated with polymyalgia rheumatica. Obstruction of medium-size arteries (e.g., temporal and ophthalmic arteries) and major branches of the aorta and the development of aortitis and aortic regurgitation are important complications of the disease. High-dose glucocorticoid therapy should be administered early and then gradually tapered. Immunosuppressive therapy with methotrexate may allow reduction in steroid dosage and reduce the risk of relapse. Tocilizumab, an interleukin-6 antagonist, demonstrated efficacy in several randomized trials. Other biologically targeted therapies are under investigation.

■ IGG4-RELATED AORTITIS

Aortitis may occur in patients with IgG4-related disease (Chap. 380) and is associated with retroperitoneal fibrosis and hydronephrosis. It can affect the thoracic and abdominal aorta, as well as the iliac arteries. Serum IgG4 levels may be elevated but are not diagnostic. Histopathologic characteristics include a lymphoplasmacytic infiltrate that comprises IgG4-positive plasma cells, fibrosis, and obliterative adventitial phlebitis; it affects men more than women and typically occurs in middle age. Glucocorticoids are used for initial treatment. Case series have reported efficacy with rituximab, an anti-CD20 monoclonal antibody. Immunosuppressive agents such as azathioprine are steroid sparing and may be effective.

■ ISOLATED AORTITIS

Isolated abdominal aortitis is characterized by adventitial and periaortic inflammation with thickening of the aortic wall; it is associated with abdominal aortic aneurysms and idiopathic retroperitoneal fibrosis. Affected individuals may present with vague constitutional symptoms, fever, and abdominal pain. Retroperitoneal fibrosis can cause ureteral obstruction and hydronephrosis. Glucocorticoids and immunosuppressive agents may reduce the inflammation.

■ RHEUMATIC AORTITIS

Rheumatoid arthritis (Chap. 370), ankylosing spondylitis (Chap. 374), psoriatic arthritis (Chap. 374), reactive arthritis (formerly known as Reiter's syndrome) (Chap. 374), relapsing polychondritis, and inflammatory bowel disorders may all be associated with aortitis involving the ascending aorta. The inflammatory lesions usually involve the ascending aorta and may extend to the sinuses of Valsalva, the mitral valve leaflets, and adjacent myocardium. The clinical manifestations are aneurysm, aortic regurgitation, and involvement of the cardiac conduction system.

■ INFECTIVE AORTITIS

Infective aortitis may result from direct invasion of the aortic wall by bacterial pathogens such as *Staphylococcus*, *Streptococcus*, and *Salmonella* or by fungi. These bacteria cause aortitis by infecting the aorta at sites of atherosclerotic plaque. Bacterial proteases lead to degradation of collagen, and the ensuing destruction of the aortic wall leads to the formation of a saccular aneurysm referred to as a mycotic aneurysm. Mycotic aneurysms have a predilection for the suprarenal abdominal aorta. The pathologic characteristics of the aortic wall include acute and chronic inflammation, abscesses, hemorrhage, and necrosis. Mycotic aneurysms typically affect the elderly and occur in men three times more frequently than in women. Patients may present with fever, sepsis, and chest, back, or abdominal pain; there may have been a preceding diarrheal illness. Blood cultures are positive in the majority of patients. Both CT and MRI are useful to diagnose mycotic aneurysms. Treatment includes antibiotic therapy and surgical removal of the affected part of the aorta and revascularization of the lower extremities with grafts placed in uninfected tissue.

Syphilitic aortitis is a late manifestation of luetic infection (Chap. 187) that usually affects the proximal ascending aorta, particularly the aortic root, resulting in aortic dilation and aneurysm formation. Syphilitic aortitis occasionally may involve the aortic arch or the descending aorta. The aneurysms may be saccular or fusiform and are usually asymptomatic, but compression of and erosion into adjacent structures may result in symptoms; rupture also may occur.

The initial lesion is an obliterative endarteritis of the vasa vasorum, especially in the adventitia. This is an inflammatory response to the invasion of the adventitia by the spirochetes. Destruction of the aortic media occurs as the spirochetes spread into this layer, usually via the lymphatics accompanying the vasa vasorum. Destruction of collagen and elastic tissues leads to dilation of the aorta, scar formation, and calcification. These changes account for the characteristic radiographic appearance of linear calcification of the ascending aorta.

The disease typically presents as an incidental chest radiographic finding 15–30 years after initial infection. Symptoms may result from aortic regurgitation, narrowing of coronary ostia due to syphilitic aortitis, compression of adjacent structures (e.g., esophagus), or rupture. Diagnosis is established by a positive serologic test, such as rapid plasmin regain (RPR), Venereal Disease Research Laboratory (VDRL), or fluorescent treponemal antibody absorption (FTA-ABS). Treatment includes penicillin and surgical excision and repair.

■ FURTHER READING

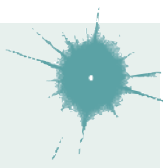
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292

Arterial Diseases of the Extremities

Mark A. Creager, Joseph Loscalzo



■ PERIPHERAL ARTERY DISEASE

Peripheral artery disease (PAD) is defined as a clinical disorder in which there is a stenosis or occlusion in the aorta or the arteries of the limbs. Atherosclerosis is the leading cause of PAD in patients >40 years old. Other causes include thrombosis, embolism, vasculitis, fibromuscular dysplasia, entrapment, cystic adventitial disease, and trauma. The highest prevalence of atherosclerotic PAD occurs in the sixth and seventh decades of life. Prevalence of PAD is similar in men and women, is greater in persons identified as black than non-Hispanic white, and is associated with lower socioeconomic status. As in patients with atherosclerosis of the coronary and cerebral vasculature, there is an increased risk of developing PAD in cigarette smokers and in persons with diabetes mellitus, hypercholesterolemia, elevated lipoprotein(a), hypertension, or renal insufficiency.

Pathology Segmental lesions that cause stenosis or occlusion are usually localized to large and medium-size vessels. The pathology of the lesions includes atherosclerotic plaques with calcium deposition, thinning of the media, patchy destruction of muscle and elastic fibers, fragmentation of the internal elastic lamina, and thrombi composed of platelets and fibrin. The primary sites of involvement are the abdominal aorta and iliac arteries (30% of symptomatic patients), the femoral and popliteal arteries (80–90% of patients), and the more distal vessels, including the tibial and peroneal arteries (40–50% of patients). Atherosclerotic lesions occur preferentially at arterial branch points, which are sites of increased turbulence, altered shear stress, and intimal injury. Involvement of the distal vasculature is most common in elderly individuals and patients with diabetes mellitus.

Clinical Evaluation Fewer than 50% of patients with PAD are symptomatic, although many have a slow or impaired gait. The most typical *symptom* is intermittent claudication, which is defined as a pain, ache, cramp, numbness, or a sense of fatigue in the muscles; it occurs during exercise and is relieved by rest. The site of claudication is distal to the location of the occlusive lesion. For example, buttock, hip, thigh, and calf discomfort occurs in patients with aortoiliac disease, whereas calf claudication develops in patients with femoral-popliteal disease. Symptoms are far more common in the lower than in the upper extremities because of the higher incidence of obstructive lesions in the former region. In patients with severe arterial occlusive disease in whom resting blood flow cannot accommodate basal nutritional needs of the tissues, chronic limb-threatening ischemia may develop. Patients complain of rest pain or a feeling of

cold or numbness in the foot and toes. Frequently, these symptoms occur at night when the legs are horizontal and improve when the legs are in a dependent position. With severe ischemia, rest pain may be persistent.

A comprehensive vascular examination includes palpation of the peripheral pulses, including the femoral, popliteal, dorsalis pedis, and posterior tibial arteries; auscultation of the abdomen and groin for bruits; and inspection of the legs and feet. Important *physical findings* of PAD include decreased or absent pulses distal to the obstruction, the presence of bruits over the narrowed artery, and muscle atrophy. With more severe disease, hair loss, thickened nails, smooth and shiny skin, reduced skin temperature, and pallor or cyanosis are common physical signs. In patients with chronic limb-threatening ischemia, ulcers or gangrene may occur. Elevation of the legs and repeated flexing of the calf muscles produce pallor of the soles of the feet, whereas rubor, secondary to reactive hyperemia, may develop when the legs are dependent. The time required for rubor to develop or for the veins in the foot to fill when the patient's legs are transferred from an elevated to a dependent position is related to the severity of the ischemia and the presence of collateral vessels. Patients with severe ischemia may develop peripheral edema because they keep their legs in a dependent position much of the time. Ischemic neuropathy can result in numbness and hyporeflexia.

Noninvasive Testing The history and physical examination are often sufficient to establish the diagnosis of PAD. An objective assessment of the presence and severity of disease is obtained by noninvasive techniques. Arterial pressure can be recorded noninvasively in the legs by placement of sphygmomanometric cuffs at the ankles and the use of a Doppler device to auscultate or record blood flow from the dorsalis pedis and posterior tibial arteries. Normally, systolic blood pressure in the legs and arms is similar. Indeed, ankle pressure may be slightly higher than arm pressure due to pulse-wave amplification. In the presence of hemodynamically significant stenoses, the systolic blood pressure in the leg is decreased. Thus, the ratio of the ankle and brachial artery systolic pressures (termed the *ankle-brachial index*, or ABI) is 1.00–1.40 in normal individuals. ABI values of 0.91–0.99 are considered “borderline,” and those ≤ 0.90 are abnormal and diagnostic of PAD. ABIs >1.40 indicate noncompressible arteries secondary to vascular calcification, as may occur in patients with diabetes mellitus or chronic kidney disease. When an ABI cannot be accurately assessed due to vascular calcification, the presence of PAD can be detected by measuring the systolic pressure of the great toe and calculating a *toe-brachial index* (TBI). A TBI of ≤ 0.70 is considered abnormal.

Other noninvasive tests include segmental pressure measurements, segmental pulse volume recordings, duplex ultrasonography (which combines B-mode imaging and Doppler flow velocity waveform analysis), transcutaneous oximetry, and stress testing (usually using a treadmill). Placement of pneumatic cuffs enables assessment of systolic pressure along the legs. The presence of pressure gradients between sequential cuffs provides evidence of the presence and location of hemodynamically significant stenoses. In addition, the amplitude of the pulse volume contour becomes blunted in the presence of significant PAD. Duplex ultrasonography is used to image and detect stenotic lesions in native arteries and bypass grafts.

Treadmill testing allows the physician to assess functional limitations objectively. Decline of the ABI immediately after exercise provides further support for the diagnosis of PAD in patients with equivocal symptoms and findings on examination.

Magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and conventional catheter-based angiography should not be used for routine diagnostic testing, but are performed before potential revascularization (Fig. 292-1). Each test is useful in defining the anatomy to assist planning for endovascular and surgical revascularization procedures.

Prognosis The natural history of patients with PAD is influenced primarily by the extent of coexisting coronary artery and cerebrovascular disease. Approximately one-third to one-half of patients with symptomatic PAD have evidence of coronary artery disease (CAD) based on clinical presentation and electrocardiogram, and over one-half have

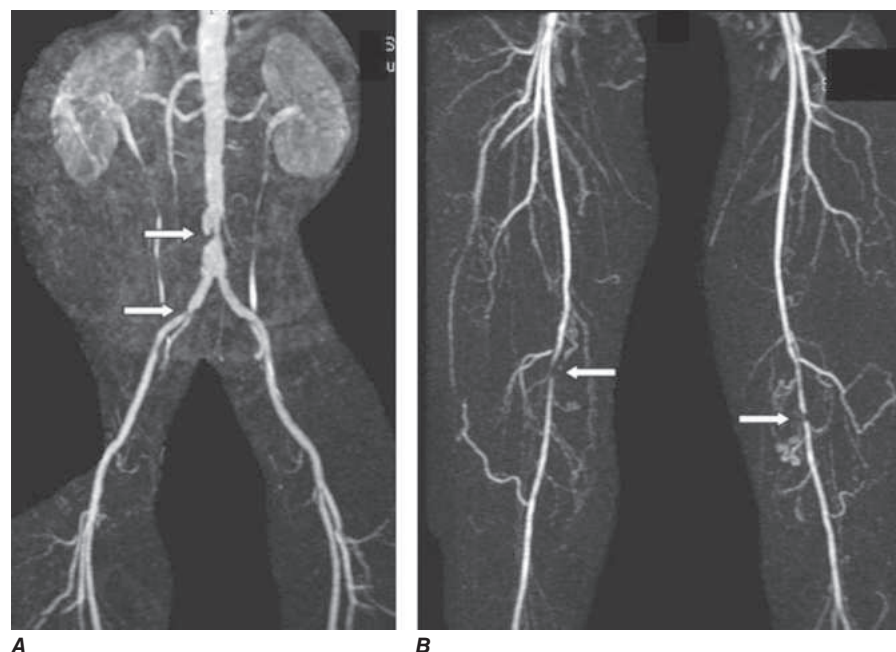


FIGURE 292-1 Magnetic resonance angiography of a patient with intermittent claudication, showing stenoses of the distal abdominal aorta and right common iliac artery (A) and stenoses of the right and left superficial femoral arteries (B). (Courtesy of Dr. Edwin Graveriaux, with permission.)

significant CAD by coronary angiography. Patients with PAD have a 15–25% 5-year mortality rate and a two- to fourfold increased risk of death from cardiovascular disease. Measurement of ABI is useful for detecting PAD and identifying persons at risk for adverse cardiovascular and limb events. Mortality rates are highest in those with the most severe PAD. The ABI worsens in almost 40% of patients, and symptoms progress in ~20–25% when assessed over a period of 5 years. Approximately 11% of patients with symptomatic PAD ultimately develop chronic limb-threatening ischemia, and without revascularization, approximately 25% of patients with chronic limb-threatening ischemia undergo amputation within 1 year. The prognosis is worse in patients who continue to smoke cigarettes or have diabetes mellitus.

TREATMENT

Peripheral Artery Disease

Patients with PAD should receive therapies to reduce the risk of associated cardiovascular events, such as myocardial infarction and death, and to improve limb symptoms, prevent progression to chronic limb-threatening ischemia, and preserve limb viability. Risk factor modification and antithrombotic therapy should be initiated to improve cardiovascular outcomes. The importance of discontinuing cigarette smoking cannot be overemphasized. The physician must assume a major role in this lifestyle modification. Counseling and adjunctive drug therapy with the nicotine patch, bupropion, or varenicline increase smoking cessation rates and reduce recidivism. It is important to control blood pressure in hypertensive patients. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may reduce the risk of cardiovascular events in patients with symptomatic PAD. β -Adrenergic blockers do not worsen claudication and may be used to treat hypertension, especially in patients with coexistent CAD. Treatment of hypercholesterolemia with statins and, if needed, adjunctive lipid-lowering agents such as ezetimibe or a PCSK9 inhibitor, are advocated to reduce the risk of myocardial infarction, stroke, and death. Statins and PCSK9 inhibitors also are associated with a decreased risk of adverse limb events, including amputation, in patients with PAD. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline on the Management of Blood Cholesterol recommends high-intensity statin treatment in patients with atherosclerotic disorders, including PAD, with the aim of achieving a 50% or greater reduction in low-density lipoprotein cholesterol.

Intensive glucose lowering reduces the risk of amputations in patients with diabetes mellitus. Among patients with diabetes and established cardiovascular disease, including PAD, the glucagon-like protein (GLP)-1 agonists and the sodium-glucose cotransporter 2 (SGLT2) inhibitors have beneficial cardiovascular effects. GLP-1 agonists also may reduce the risk of amputation. Platelet inhibitors, including aspirin and the adenosine diphosphate (ADP) antagonist clopidogrel, reduce the risk of adverse cardiovascular events in patients with atherosclerosis and are recommended for patients with symptomatic PAD, including those with intermittent claudication or chronic limb-threatening ischemia or prior lower extremity revascularization. Outcomes with ticagrelor are similar to those with clopidogrel. The benefit of dual antiplatelet therapy with both aspirin and clopidogrel compared with aspirin alone in reducing cardiovascular morbidity and mortality rates in patients with PAD is uncertain. When added to other antiplatelet therapy, vorapaxar, a protease-activated receptor-1 antagonist that inhibits thrombin-mediated platelet activation, decreases the risk of adverse cardiovascular events in patients with atherosclerosis, including PAD. It also reduces the risk of acute limb ischemia and peripheral revascularization; however, it is associated with an increased rate of moderate bleeding. The anticoagulant warfarin is as effective as antiplatelet therapy in preventing adverse cardiovascular events but causes more major bleeding; therefore, it is not indicated to improve outcomes in patients with chronic PAD. The combination of a low dose of the oral factor Xa inhibitor rivaroxaban and aspirin improves cardiovascular and limb outcomes in patients with atherosclerosis, including those with established PAD, as well as those who have undergone peripheral revascularization, but is associated with increased risk of bleeding.

Therapies for intermittent claudication and chronic limb-threatening ischemia include supportive measures, medications, exercise training, endovascular interventions, and surgery. Supportive measures include meticulous care of the feet, which should be kept clean and protected against excessive drying with moisturizing creams. Well-fitting and protective shoes are advised to reduce trauma. Elastic support hose should be avoided, as it reduces blood flow to the skin. In patients with chronic limb-threatening ischemia, shock blocks under the head of the bed together with a canopy over the feet may improve perfusion pressure and ameliorate some of the rest pain.

Patients with claudication should be encouraged to exercise regularly and at progressively more strenuous levels. Supervised exercise

training programs for 30- to 45-min sessions, at least three times per week for 12 weeks, prolong walking distance. The beneficial effect of supervised exercise training on walking performance in patients with claudication often is similar to or greater than that realized after a revascularization procedure. Structured home and community-based exercise programs are also effective. Pharmacologic treatment of PAD has not been as successful as the medical treatment of CAD (**Chap. 284**). In particular, vasodilators as a class have not proved to be beneficial. During exercise, peripheral vasodilation occurs distal to sites of significant arterial stenoses. As a result, perfusion pressure falls, often to levels lower than those generated in the interstitial tissue by the exercising muscle. Drugs such as α -adrenergic blocking agents, calcium channel antagonists, and other vasodilators have not been shown to be effective in patients with PAD.

Cilostazol, a phosphodiesterase-3 inhibitor with vasodilator and antiplatelet properties, increases claudication distance by 40–60% and improves measures of quality of life. The mechanism of action accounting for its beneficial effects is not known. Pentoxifylline, a substituted xanthine derivative, increases blood flow to the microcirculation and enhances tissue oxygenation. Although several placebo-controlled studies have found that pentoxifylline modestly increases the duration of exercise, its efficacy has not been confirmed in other clinical trials. Statins appeared effective for treatment of intermittent claudication in initial clinical trials, but more studies are needed to confirm the efficacy of this class of drugs.

There is no definitive medical therapy for chronic limb-threatening ischemia. Vasodilators, including prostaglandins, are not effective in relieving symptoms or preventing limb loss. Enthusiasm for therapy with angiogenic growth factors abated when clinical trials of intramuscular gene transfer of DNA encoding vascular endothelial growth factor, fibroblast growth factor, hepatocyte growth factor, or hypoxia-inducible factor 1 α failed to demonstrate improvement in symptoms or outcomes in patients with intermittent claudication or critical limb ischemia. Most clinical trials of bone marrow–derived vascular progenitor cells to promote angiogenesis and preserve limb viability in patients with critical limb ischemia have failed to demonstrate benefit, although a meta-analysis of these trials suggested a modest reduction in the risk of amputation.

REVASCULARIZATION

Revascularization procedures, including catheter-based, open surgical, and hybrid interventions, are indicated for patients with chronic limb-threatening ischemia to relieve pain and prevent limb loss. These procedures are also indicated for patients with disabling, progressive, or severe symptoms of intermittent claudication despite medical therapy in order to improve walking distance and functional capacity. When revascularization is performed in conjunction with a supervised exercise program, walking distance improves more than with exercise training alone. MRA, CTA, or conventional angiography should be performed to assess vascular anatomy in patients who are being considered for revascularization.

Endovascular interventions include percutaneous transluminal balloon angioplasty (PTA) (including drug-coated balloons), stent placement (including drug-eluting stents), stent grafts, and atherectomy (**Chap. 287**). Several operative procedures are available for treating patients with PAD. The preferred operative procedure depends on the location and extent of the obstruction(s) and the general medical condition of the patient. Operative procedures for aortoiliac disease include aortobifemoral bypass, axillofemoral bypass, femoro-femoral bypass, and aortoiliac endarterectomy. Operative therapy for femoral-popliteal and tibioperoneal artery disease includes in situ and reverse autogenous saphenous vein bypass grafts, placement of polytetrafluoroethylene (PTFE) or other synthetic grafts, and thromboendarterectomy. The decision to use an endovascular, open surgical, or a hybrid revascularization strategy depends on the vascular anatomy, including the location and extent of the arterial occlusions, the availability of suitable saphenous vein segments, comorbidities, and the skill and experience of the operator.

Preoperative cardiac risk assessment may identify individuals who are especially likely to experience an adverse cardiac event during the perioperative period. Patients with angina, prior myocardial infarction, heart failure, diabetes, or renal insufficiency are among those at increased risk. Stress testing with treadmill exercise (if feasible), radionuclide myocardial perfusion imaging, or echocardiography permits further stratification of risk in these patients, particularly those with poor or unknown functional capacity (**Chap. 287**). Patients with abnormal test results require close supervision and adjunctive management with anti-ischemic medications. Coronary angiography and coronary artery revascularization compared with optimal medical therapy do not improve outcomes in most patients undergoing peripheral vascular surgery, but cardiac catheterization should be considered in patients with unstable angina and angina refractory to medical therapy as well as those suspected of having left main or three-vessel CAD.

■ FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia (FMD) is a hyperplastic disorder that typically affects medium-size and small arteries, but it can also affect larger arteries. The most common histologic characteristics include medial deposition of collagen causing fibromuscular ridges alternating with areas of thinned media. FMD occurs predominantly in females and usually involves the renal and carotid/vertebral arteries but can involve coronary and mesenteric arteries, as well as extremity vessels such as the iliac and subclavian arteries. FMD may cause stenosis, dissection, aneurysm, or thrombosis in affected arteries. When limb vessels are involved, clinical manifestations are similar to those for atherosclerosis, including claudication and rest pain.

A contemporary classification based on the angiographic appearance divides FMD into two types: multifocal, identified by a “string of beads” appearance caused by the thickened fibromuscular ridges contiguous with thin, less-involved portions of the arterial wall; and focal, identified as either unifocal (<1 cm) or tubular ($\geq$ 1 cm) stenoses.

Aspirin is recommended to reduce the risk of thrombosis in affected vessels. PTA and surgical reconstruction are beneficial in patients with debilitating symptoms or threatened limbs.

■ THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (Buerger's disease) is an inflammatory occlusive vascular disorder involving small and medium-size arteries and veins in the distal upper and lower extremities. Cerebral, visceral, and coronary vessels may be affected rarely. This disorder develops most frequently in men <40 years of age. The prevalence is higher in Asians and individuals of Eastern European descent. Although the cause of thromboangiitis obliterans is not known, there is a definite relationship to cigarette smoking in patients with this disorder.

In the initial stages of thromboangiitis obliterans, polymorphonuclear leukocytes infiltrate the walls of the small and medium-size arteries and veins. The internal elastic lamina is preserved, and a cellular, inflammatory thrombus develops in the vascular lumen. As the disease progresses, mononuclear cells, fibroblasts, and giant cells replace the neutrophils. Later stages are characterized by perivascular fibrosis, organized thrombus, and recanalization.

The clinical features of thromboangiitis obliterans often include a triad of claudication of the affected extremity, Raynaud phenomenon, and migratory superficial vein thrombophlebitis. Claudication usually is confined to the calves and feet or the forearms and hands because this disorder primarily affects distal vessels. In the presence of severe digital ischemia, trophic nail changes, painful ulcerations, and gangrene may develop at the tips of the fingers or toes. The physical examination shows normal brachial and popliteal pulses but reduced or absent radial, ulnar, and/or tibial pulses. MRA, CTA, and conventional arteriography are helpful in making the diagnosis. Smooth, tapering segmental lesions in the distal vessels are characteristic, as are collateral vessels at sites of vascular occlusion. Proximal atherosclerotic disease is usually absent. The diagnosis can

be confirmed by excisional biopsy and pathologic examination of an involved vessel.

There is no specific treatment except abstention from tobacco. The prognosis is worse in individuals who continue to smoke, but results are discouraging even in those who stop smoking. Arterial bypass of the larger vessels may be used in selected instances, as well as local debridement, depending on the symptoms and severity of ischemia. Antibiotics may be useful; anticoagulants and glucocorticoids are not helpful. If these measures fail, amputation may be required.

■ OTHER VASCULITIDES

Other vasculitides may affect the arteries that supply the upper and lower extremities. **Takayasu arteritis and giant cell (temporal) arteritis are discussed in Chap. 375.**

■ ACUTE LIMB ISCHEMIA

Acute limb ischemia occurs when arterial occlusion results in the sudden cessation of blood flow to an extremity. The severity of ischemia and the viability of the extremity depend on the location and extent of the occlusion and the presence and subsequent development of collateral blood vessels. Principal causes of acute arterial occlusion include embolism, thrombus in situ, arterial dissection, and trauma.

The most common sources of arterial emboli are the heart, aorta, and large arteries. Cardiac disorders that cause thromboembolism include atrial fibrillation; acute myocardial infarction; ventricular aneurysm; cardiomyopathy; infectious and marantic endocarditis; thrombi associated with prosthetic heart valves; and atrial myxoma. Emboli to the distal vessels may also originate from proximal sites of atherosclerosis and aneurysms of the aorta and large vessels. Less frequently, an arterial occlusion results paradoxically from a venous thrombus that has entered the systemic circulation via a patent foramen ovale or another septal defect. Arterial emboli tend to lodge at vessel bifurcations because the vessel caliber decreases at those sites; in the lower extremities, emboli lodge most frequently in the femoral artery, followed by the iliac artery, aorta, and popliteal and tibioperoneal arteries.

Acute arterial thrombosis in situ occurs most frequently in atherosclerotic vessels at the site of an atherosclerotic plaque or aneurysm and in arterial bypass grafts. Trauma to an artery may disrupt continuity of blood flow and cause acute limb ischemia via formation of an acute arterial thrombus or by disruption of an artery's integrity and extravasation of blood. Arterial occlusion may complicate arterial punctures and placement of catheters; it also may result from arterial dissection if the intimal flap obstructs the artery. Less common causes include thoracic outlet compression syndrome, which causes subclavian artery occlusion, and entrapment of the popliteal artery by abnormal placement of the medial head of the gastrocnemius muscle. Polycythemia and hypercoagulable disorders (**Chaps. 108 and 121**) are also associated with acute arterial thrombosis.

■ CLINICAL FEATURES

The symptoms of an acute arterial occlusion depend on the location, duration, and severity of the obstruction. Often severe pain, paresthesia, numbness, and coldness develop in the involved extremity within 1 h. Paralysis may occur with severe and persistent ischemia. Physical findings include loss of pulses distal to the occlusion, cyanosis or pallor, mottling, decreased skin temperature, muscle stiffening, loss of sensation, weakness, and/or absent deep tendon reflexes. If acute arterial occlusion occurs in the presence of an adequate collateral circulation, as is often the case in acute graft occlusion, the symptoms and findings may be less severe. In this situation, the patient complains about an abrupt decrease in the distance walked before claudication occurs or of modest pain and paresthesia. Pallor and coolness are evident, but sensory and motor functions generally are preserved. The clinical evaluation includes Doppler assessment of peripheral blood flow. The diagnosis of acute limb ischemia is usually apparent from the clinical presentation. In most circumstances, duplex ultrasound, MRA, CTA, or catheter-based arteriography is used to confirm the diagnosis and demonstrate the location and extent of arterial occlusion.

TREATMENT

Acute Limb Ischemia

Once the diagnosis is made, the patient should be anticoagulated with intravenous heparin to prevent propagation of the clot and recurrent embolism. In cases of severe ischemia of recent onset, particularly when limb viability is jeopardized, immediate intervention to ensure reperfusion is indicated. Catheter-directed thrombolysis/thrombectomy, surgical thromboembolectomy, and arterial bypass procedures are used to restore blood flow to the ischemic extremity promptly, particularly when a large proximal vessel is occluded.

Intraarterial thrombolytic therapy with recombinant tissue plasminogen activator, reteplase, or tenecteplase is most effective when acute arterial occlusion is recent and caused by a thrombus in an atherosclerotic vessel, arterial bypass graft, or occluded stent. Thrombolytic therapy is also indicated when the patient's overall condition contraindicates surgical intervention or when smaller distal vessels are occluded, thus preventing surgical access. Meticulous observation for hemorrhagic complications is required during intraarterial thrombolytic therapy. Ultrasound-emitting catheters may accelerate reperfusion by improving thrombus permeability to thrombolytic agents. Another endovascular approach to thrombus removal is percutaneous mechanical thrombectomy using devices that employ hydrodynamic forces or rotating baskets to fragment and remove the clot. These treatments may be used alone but usually are used in conjunction with pharmacologic thrombolysis. Surgical revascularization is preferred when restoration of blood flow must occur within 24 h to prevent limb loss. Amputation is performed when the limb is not viable, as characterized by loss of sensation, paralysis, and the absence of Doppler-detected blood flow in both arteries and veins.

Long-term anticoagulation is indicated when acute limb ischemia is caused by cardiac thromboembolism. Emboli resulting from infective endocarditis, the presence of prosthetic heart valves, or atrial myxoma often require surgical intervention to remove the cause.

■ ATHEROEMBOLISM

Atheroembolism is another cause of limb ischemia. In this condition, multiple small deposits of fibrin, platelets, and cholesterol debris embolize from proximal atherosclerotic lesions or aneurysmal sites. Large protruding aortic atheromas are a source of emboli that may lead to limb ischemia, as well as stroke and renal insufficiency. Atheroembolism may occur after intraarterial procedures. Since atheroemboli to limbs tend to lodge in the small vessels of the muscle and skin and may not occlude the large vessels, distal pulses usually remain palpable. Patients complain of acute pain and tenderness at the site of embolization. Digital vascular occlusion may result in ischemia and the "blue toe" syndrome; digital necrosis and gangrene may develop (**Fig. 292-2**). Localized areas of tenderness, pallor, and livedo reticularis (see below) occur at sites of emboli. Skin or muscle biopsy may demonstrate cholesterol crystals.

Ischemia resulting from atheroemboli is notoriously difficult to treat. Local foot care and occasionally amputation may be needed to treat necrotic areas. Analgesics are indicated for pain relief. Usually neither surgical revascularization procedures nor thrombolytic therapy is helpful because of the multiplicity, composition, and distal location of the emboli. Therapy with antiplatelet drugs and statins improves cardiovascular outcome in patients with atherosclerosis, but it is not established whether either class of drugs prevents recurrent atheroembolism. Similarly, it is not known whether anticoagulant therapy is effective. Endovascular or surgical intervention to exclude or bypass the atherosclerotic vessel or aneurysm that causes the recurrent atheroemboli may be necessary.

■ THORACIC OUTLET COMPRESSION SYNDROME

This is a symptom complex resulting from compression of the neurovascular bundle (artery, vein, or nerves) at the thoracic outlet as it



FIGURE 292-2 Atheroembolism causing cyanotic discoloration and impending necrosis of the toes ("blue toe" syndrome).

courses through the neck and shoulder. Cervical ribs, abnormalities of the scalenus anticus muscle, proximity of the clavicle to the first rib, or abnormal insertion of the pectoralis minor muscle may compress the subclavian artery, subclavian vein, and brachial plexus as these structures pass from the thorax to the arm. Depending on the structures affected, thoracic outlet compression syndrome is divided into arterial, venous, and neurogenic forms. Patients with neurogenic thoracic outlet compression may develop shoulder and arm pain, weakness, and paresthesias. Patients with arterial compression may experience claudication, Raynaud phenomenon, and even ischemic tissue loss and gangrene. Venous compression may cause thrombosis of the subclavian and axillary veins; this is often associated with effort and is referred to as *Paget-Schroetter syndrome*.

APPROACH TO THE PATIENT

Arterial Thoracic Outlet Compression Syndrome

Examination of a patient with arterial thoracic outlet compression syndrome is often normal unless provocative maneuvers are performed. Occasionally, distal pulses are decreased or absent and digital cyanosis and ischemia may be evident.

Several maneuvers that support the diagnosis of arterial thoracic outlet compression syndrome may be used to precipitate symptoms, cause a subclavian artery bruit, and diminish arm pulses. These maneuvers include the abduction and external rotation test, in which the affected arm is abducted by 90° and the shoulder is externally rotated; the scalene maneuver (extension of the neck and rotation of the head to the side of the symptoms); the costoclavicular maneuver (posterior rotation of shoulders); and the hyperabduction maneuver (raising the arm 180°). A chest x-ray will indicate the presence of cervical ribs. Duplex ultrasonography, CTA, MRA, and contrast angiography can be performed during provocative maneuvers to demonstrate thoracic outlet compression of the subclavian artery. Neurophysiologic tests such as the electromyogram, nerve conduction studies, and somatosensory evoked potentials may be abnormal if the brachial plexus is involved, but the diagnosis of neurogenic thoracic outlet syndrome is not necessarily excluded if these tests are normal owing to their low sensitivity.

Most patients can be managed conservatively. They should be advised to avoid the positions that cause symptoms. Many patients benefit from shoulder girdle exercises. Surgical procedures such as removal of the first rib and resection of the scalenus anticus muscle are necessary occasionally for relief of symptoms or treatment of ischemia.

POPLITEAL ARTERY ENTRAPMENT

Popliteal artery entrapment typically affects young athletic men and women when the gastrocnemius or popliteus muscle compresses the popliteal artery and causes intermittent claudication. Thrombosis, embolism, or popliteal artery aneurysm may occur. The pulse examination may be normal unless provocative maneuvers such as ankle dorsiflexion and plantar flexion are performed. The diagnosis is confirmed by duplex ultrasound, CTA, MRA, or conventional angiography. Treatment involves surgical release of the popliteal artery or vascular reconstruction.

POPLITEAL ARTERY ANEURYSM

Popliteal artery aneurysms are the most common peripheral artery aneurysms. Approximately 50% are bilateral. Patients with popliteal artery aneurysms often have aneurysms of other arteries, especially the aorta. The most common clinical presentation is limb ischemia secondary to thrombosis or embolism. Rupture occurs less frequently. Other complications include compression of the adjacent popliteal vein or peroneal nerve. Popliteal artery aneurysm can be detected by palpation and confirmed by duplex ultrasonography. Repair is indicated for symptomatic aneurysms or when the diameter exceeds 2–3 cm, owing to the risk of thrombosis, embolism, or rupture.

ARTERIOVENOUS FISTULA

Abnormal communications between an artery and a vein, bypassing the capillary bed, may be congenital or acquired. Congenital arteriovenous fistulas are a result of persistent embryonic vessels that fail to differentiate into arteries and veins; they may be associated with birthmarks, can be located in almost any organ of the body, and frequently occur in the extremities. Acquired arteriovenous fistulas either are created to provide vascular access for hemodialysis or occur as a result of a penetrating injury such as a gunshot or knife wound or as complications of arterial catheterization or surgical dissection. An uncommon cause of arteriovenous fistula is rupture of an arterial aneurysm into a vein.

The clinical features depend on the location and size of the fistula. Frequently, a pulsatile mass is palpable, and a thrill and a bruit lasting throughout systole and diastole are present over the fistula. With long-standing fistulas, clinical manifestations of chronic venous insufficiency, including peripheral edema; large, tortuous varicose veins; and stasis pigmentation become apparent because of the high venous pressure. Evidence of ischemia may occur in the distal portion of the extremity. Skin temperature is higher over the arteriovenous fistula. Large arteriovenous fistulas may result in an increased cardiac output with consequent cardiomegaly and high-output heart failure (**Chap. 264**).

The diagnosis is often evident from the physical examination. Compression of a large arteriovenous fistula may cause reflex slowing of the heart rate (Nicoladoni-Branham sign). Duplex ultrasonography may detect an arteriovenous fistula, especially one that affects the femoral artery and vein at the site of catheter access. CTA and conventional angiography can confirm the diagnosis and are useful in demonstrating the site and size of the arteriovenous fistula.

Management of arteriovenous fistulas may involve surgery, radiotherapy, or embolization. Congenital arteriovenous fistulas are often difficult to treat because the communications may be numerous and extensive, and new communications frequently develop after ligation of the most obvious ones. Many of these lesions are best treated conservatively using elastic support hose to reduce the consequences of venous hypertension. Occasionally, embolization with autologous material, such as fat or muscle, or with hemostatic agents, such as gelatin sponges or silicon spheres, is used to obliterate the fistula. Acquired arteriovenous fistulas are usually amenable to surgical treatment that involves division or excision of the fistula. Occasionally, autogenous or synthetic grafting is necessary to reestablish continuity of the artery and vein.

RAYNAUD PHENOMENON

Raynaud phenomenon is characterized by episodic digital ischemia, manifested clinically by the sequential development of digital



FIGURE 292-3 Vascular diseases associated with temperature: **A.** Raynaud phenomenon; **B.** acrocyanosis; **C.** livedo reticularis; **D.** pernio; **E.** erythromelalgia; and **F.** frostbite.

blanching, cyanosis, and rubor of the fingers or toes after cold exposure and subsequent rewarming. Emotional stress may also precipitate Raynaud phenomenon. The color changes are usually well demarcated and are confined to the fingers or toes. Typically, one or more digits will appear white when the patient is exposed to a cold environment or touches a cold object (Fig. 292-3A). The blanching, or pallor, represents the ischemic phase of the phenomenon and results from vasospasm of digital arteries. During the ischemic phase, capillaries and venules dilate, and cyanosis results from the deoxygenated blood that is present in these vessels. A sensation of cold or numbness or paresthesia of the digits often accompanies the phases of pallor and cyanosis.

With rewarming, the digital vasospasm resolves, and blood flow into the dilated arterioles and capillaries increases dramatically. This “reactive hyperemia” imparts a bright red color to the digits. In addition to rubor and warmth, patients often experience a throbbing, painful sensation during the hyperemic phase. Although the triphasic color response is typical of Raynaud phenomenon, some patients may develop only pallor and cyanosis; others may experience only cyanosis.

Raynaud phenomenon is broadly separated into two categories: idiopathic, termed primary Raynaud phenomenon, and secondary Raynaud phenomenon, which is associated with other disease states or known causes of vasospasm (Table 292-1).

Primary Raynaud Phenomenon This appellation is applied when the secondary causes of Raynaud phenomenon have been excluded. Over 50% of patients with Raynaud phenomenon have the primary form. Women are affected about five times more often than men, and the age of presentation is usually between 20 and 40 years. The fingers are involved more frequently than the toes. Initial episodes may involve only one or two fingertips, but subsequent attacks may involve the entire finger and may include all the fingers. The toes are affected in 40% of patients. Although vasospasm of the toes usually occurs in patients with symptoms in the fingers, it may happen alone.

Rarely, the earlobes, the tip of the nose, tongue, nipple, or penis are involved. Raynaud phenomenon occurs frequently in patients who also have migraine headaches or variant angina from coronary vasospasm. These associations suggest that there may be a common predisposing cause for the vasospasm.

Results of physical examination are often entirely normal; the radial, ulnar, and pedal pulses are normal. The fingers and toes may be cool between attacks and may perspire excessively. Nailfold capillaroscopy reveals normal superficial capillaries, which appear as regularly spaced hairpin loops. Thickening and tightening of the digital subcutaneous tissue (*sclerodactyly*) develop in 10% of patients. Angiography of the digits for diagnostic purposes is not indicated.

TABLE 292-1 Classification of Raynaud Phenomenon

Primary or idiopathic Raynaud phenomenon

Secondary Raynaud phenomenon

Collagen vascular diseases: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis, mixed connective tissue disease, Sjögren syndrome

Arterial occlusive diseases: atherosclerosis of the extremities, thromboangiitis obliterans, acute arterial occlusion, thoracic outlet syndrome

Pulmonary hypertension

Neurologic disorders: intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome, complex regional pain syndrome

Blood dyscrasias: cold agglutinins, cryoglobulinemia, cryofibrinogenemia, myeloproliferative disorders, lymphoplasmacytic lymphoma

Trauma: vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing

Drugs and toxins: ergot derivatives, methysergide, β -adrenergic receptor blockers, bleomycin, vinblastine, cisplatin, gemcitabine, vinyl chloride

In general, patients with primary Raynaud disease have milder clinical manifestations. Fewer than 1% of these patients lose a part of a digit. After the diagnosis is made, the disease improves spontaneously in ~15% of patients and progresses in ~30%.

Secondary Causes of Raynaud Phenomenon Raynaud phenomenon occurs in 80–90% of patients with systemic sclerosis (scleroderma) and is the presenting symptom in 30% (Chap. 372). It may be the only symptom of scleroderma for many years. Abnormalities of the digital vessels may contribute to the development of Raynaud phenomenon in this disorder. Ischemic fingertip ulcers may develop and progress to gangrene and amputation. About 20% of patients with systemic lupus erythematosus (SLE) have Raynaud phenomenon (Chap. 368). Occasionally, persistent digital ischemia develops and may result in ulcers or gangrene. In most severe cases, the small vessels are occluded by a proliferative endarteritis. Raynaud phenomenon occurs in ~30% of patients with dermatomyositis or polymyositis (Chap. 377). It frequently develops in patients with rheumatoid arthritis and may be related to the intimal proliferation that occurs in the digital arteries.

Atherosclerosis of the extremities is a common cause of Raynaud phenomenon in men aged >50 years. Thromboangiitis obliterans is an uncommon cause of Raynaud phenomenon but should be considered in young men, particularly those who are cigarette smokers. The development of cold-induced pallor in these disorders may be confined to one or two digits of the involved extremity. Occasionally, Raynaud phenomenon may follow acute occlusion of large and medium-sized arteries by a thrombus or embolus. Embolization of atheroembolic debris may cause digital ischemia. The latter situation often involves one or two digits and should not be confused with Raynaud phenomenon. In patients with thoracic outlet compression syndrome, Raynaud phenomenon may result from diminished intravascular pressure, stimulation of sympathetic fibers in the brachial plexus, or a combination of both. Raynaud phenomenon occurs in patients with primary pulmonary hypertension (Chap. 294); this is more than coincidental and may reflect a neurohumoral abnormality that affects both the pulmonary and digital circulations.

A variety of blood dyscrasias may be associated with Raynaud phenomenon. Cold-induced precipitation of plasma proteins, hyperviscosity, and aggregation of red cells and platelets may occur in patients with cold agglutinins, cryoglobulinemia, or cryofibrinogenemia. Hyperviscosity syndromes that accompany myeloproliferative disorders and lymphoplasmacytic lymphoma (Waldenström macroglobulinemia) should also be considered in the initial evaluation of patients with Raynaud phenomenon.

Raynaud phenomenon occurs often in patients whose vocations require the use of vibrating hand tools, such as chain saws or jackhammers. The frequency of Raynaud phenomenon also seems to be increased in pianists and keyboard operators. Electric shock injury to the hands or frostbite may lead to the later development of Raynaud phenomenon.

Several drugs have been causally implicated in Raynaud phenomenon. They include ergot preparations, methysergide, β -adrenergic receptor antagonists, and the chemotherapeutic agents bleomycin, vinblastine, cisplatin, and gemcitabine.

TREATMENT

Raynaud Phenomenon

Most patients with Raynaud phenomenon experience only mild and infrequent episodes. These patients need reassurance and should be instructed to dress warmly and avoid unnecessary cold exposure. In addition to gloves and mittens, patients should protect the trunk, head, and feet with warm clothing to prevent cold-induced reflex vasoconstriction. Tobacco use is contraindicated.

Drug treatment should be reserved for severe cases. Dihydropyridine calcium channel antagonists such as nifedipine and amlodipine decrease the frequency and severity of Raynaud phenomenon. Diltiazem may be considered but is less effective. The postsynaptic α_1 -adrenergic antagonist prazosin has been used with

favorable responses; doxazosin and terazosin may also be effective. Phosphodiesterase type 5 inhibitors such as sildenafil, tadalafil, and vardenafil may improve symptoms in patients with secondary Raynaud phenomenon, as occurs with systemic sclerosis. There is also evidence that topical nitroglycerin preparations are effective. Digital sympathectomy is helpful in some patients who are unresponsive to medical therapy. Injection of botulinum toxin into the perivascular tissue of the wrist or palm improved ischemic manifestations of severe Raynaud phenomenon in case series, although controlled clinical trials have yielded inconsistent results.

ACROCYNANOSIS

In this condition, there is arterial vasoconstriction and secondary dilation of the capillaries and venules with resulting persistent cyanosis of the hands and, less frequently, the feet. Cyanosis may be intensified by exposure to a cold environment. Acrocyanosis may be categorized as primary or secondary to an underlying condition. In primary acrocyanosis, women are affected much more frequently than men, and the age of onset is usually <30 years. Generally, patients are asymptomatic but seek medical attention because of the discoloration. The prognosis is favorable, and pain, ulcers, and gangrene do not occur. Examination reveals normal pulses, peripheral cyanosis, and moist palms (Fig. 292-3B). Trophic skin changes and ulcerations do not occur. The disorder can be distinguished from Raynaud phenomenon because it is persistent and not episodic, the discoloration extends proximally from the digits, and blanching does not occur. Ischemia secondary to arterial occlusive disease can usually be excluded by the presence of normal pulses. Central cyanosis and decreased arterial oxygen saturation are not present. Patients should be reassured and advised to dress warmly and avoid cold exposure. Pharmacologic intervention is not indicated.

Secondary acrocyanosis may result from hypoxemia, vasopressor medications, connective tissue diseases, atheroembolism, antiphospholipid antibodies, cold agglutinins, or cryoglobulins and is associated with anorexia nervosa and postural orthostatic tachycardia syndrome. Treatment should be directed at the underlying disorder.

LIVEDO RETICULARIS

In this condition, localized areas of the extremities develop a mottled or rete (netlike) appearance of reddish to blue discoloration (Fig. 293-3C). There are primary and secondary forms of livedo reticularis. The primary, or idiopathic, form of this disorder may be benign or associated with ulcerations. The benign form occurs more frequently in women than in men, and the most common age of onset is the third decade. The mottling typically is symmetric and uniform and may be more prominent after cold exposure and improve with warming. Patients with the benign form are usually asymptomatic and seek attention for cosmetic reasons. These patients should be reassured and advised to avoid cold environments. No drug treatment is indicated. Primary livedo reticularis with ulceration is also called *atrophie blanche en plaque*. The ulcers are painful and may take months to heal. Secondary livedo reticularis can occur with atheroembolism (see above), SLE and other vasculitides, antiphospholipid antibodies, hyperviscosity, cryoglobulinemia, and Sneddon's syndrome (ischemic stroke and livedo reticularis). Livedo racemosa is the term used to characterize secondary livedo reticularis, when the mottling is irregular and disrupted, and does not improve with warming. Rarely, skin ulcerations develop.

PERNIO (CHILBLAINS)

Pernio is a vasculitic disorder associated with exposure to cold; acute forms have been described. Raised erythematous lesions develop most commonly on the toes or fingers in cold weather (Fig. 292-3D). They are associated with pruritus and a burning sensation, and they may blister and ulcerate. Pathologic examination demonstrates angitis characterized by intimal proliferation and perivascular infiltration of mononuclear and polymorphonuclear leukocytes. Giant cells may be present in the subcutaneous tissue. Patients should avoid exposure to cold, and ulcers should be kept clean and protected with sterile dressings. Sympatholytic drugs and dihydropyridine calcium channel antagonists may be effective in some patients.

■ ERYTHROMELALGIA

This disorder is characterized by burning pain and erythema of the extremities (Fig. 292-3E). The feet are involved more frequently than the hands, and males are affected more frequently than females. Erythromelalgia may occur at any age but is most common in middle age. It may be primary (also termed erythermalgia) or secondary. Mutations in the SCN9A gene, which encodes the Nav1.7 voltage-gated sodium channel expressed in sensory and sympathetic nerves, have been described in inherited forms of erythromelalgia. The most common causes of secondary erythromelalgia are myeloproliferative disorders such as polycythemia vera and essential thrombocytosis. Less common causes include drugs, such as calcium channel blockers, bromocriptine, and pergolide; neuropathies; connective tissue diseases such as SLE; and paraneoplastic syndromes. Patients complain of burning in the extremities that is precipitated by exposure to a warm environment and aggravated by a dependent position. The symptoms are relieved by exposing the affected area to cool air or water or by elevation. Erythromelalgia can be distinguished from ischemia secondary to peripheral arterial disorders because the peripheral pulses are present. There is no specific treatment; aspirin may produce relief in patients with erythromelalgia secondary to myeloproliferative disease. Topical anesthetics, such as lidocaine, or a combination of amitriptyline and ketamine may be considered to relieve pain. Topical midodrine may also be considered. Treatment of associated disorders in secondary erythromelalgia may be helpful.

■ FROSTBITE

In this condition, tissue damage results from severe environmental cold exposure or from direct contact with a very cold object. Tissue injury results from both freezing and vasoconstriction. Frostbite usually affects the distal aspects of the extremities or exposed parts of the face, such as the ears, nose, chin, and cheeks. Superficial frostbite involves the skin and subcutaneous tissue. Patients experience pain or paresthesia, and the skin appears white and waxy. After rewarming, there is cyanosis and erythema, wheal-and-flare formation, edema, and superficial blisters. Deep frostbite involves muscle, nerves, and deeper blood vessels. It may result in edema of the hand or foot, vesicles and bullae, tissue necrosis, and gangrene (Fig. 292-3F).

Initial treatment is rewarming, performed in an environment where reexposure to freezing conditions will not occur. Rewarming is accomplished by immersion of the affected part in a water bath at temperatures of 40°–44°C (104°–111°F). Massage, application of ice water, and extreme heat are contraindicated. The injured area should be cleansed with soap or antiseptic, and sterile dressings should be applied. Analgesics are often required during rewarming. Antibiotics are used if there is evidence of infection. The efficacy of sympathetic blocking drugs is not established. After recovery, the affected extremity may exhibit increased sensitivity to cold.

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293

Chronic Venous Disease and Lymphedema

Mark A. Creager, Robert T. Eberhardt,
Joseph Loscalzo

■ CHRONIC VENOUS DISEASE

Chronic venous diseases range from telangiectasias and reticular veins, to varicose veins, to chronic venous insufficiency with edema, skin changes, and ulceration. This section of the chapter will focus on identification and treatment of varicose veins and chronic venous insufficiency, since these problems are encountered frequently by the internist. The estimated prevalence of varicose veins in the United States is ~15% in men and 30% in women. Chronic venous insufficiency with edema affects ~7.5% of men and 5% of women, and the prevalence increases with age ranging from 2% among those <50 years of age to 10% of those 70 years of age. Approximately 20% of patients with chronic venous insufficiency develop venous ulcers.

■ VENOUS ANATOMY

Veins in the extremities can be broadly classified as either superficial or deep. The superficial veins are located between the skin and deep fascia. In the legs, these include the great and small saphenous veins and their tributaries. The great saphenous vein is the longest vein in the body. It originates on the medial side of the foot and ascends anterior to the medial malleolus and then along the medial side of the calf and thigh and drains into the common femoral vein. The small saphenous vein originates on the dorsolateral aspect of the foot, ascends posterior to the lateral malleolus and along the posterolateral aspect of the calf, and drains into the popliteal vein. The deep veins of the leg accompany the major arteries. There are usually paired peroneal, anterior tibial, and posterior tibial veins in the calf, which converge to form the popliteal vein. Soleal tributary veins drain into the posterior tibial or peroneal veins, and gastrocnemius tributary veins drain into the popliteal vein. The popliteal vein ascends in the thigh as the femoral vein. The confluence of the femoral vein and deep femoral vein form the common femoral vein, which ascends in the pelvis as the external iliac and then common iliac vein, which converges with the contralateral common iliac vein at the inferior vena cava. Perforating veins connect the superficial and deep systems in the legs at multiple locations, normally allowing blood to flow from the superficial to deep veins. In the arms, the superficial veins include the basilic, cephalic, and median cubital veins and their tributaries. The basilic and cephalic veins course along the medial and lateral aspects of the arm, respectively, and these are connected via the median cubital vein in the antecubital fossa. The deep veins of the arms accompany the major arteries and include the radial, ulnar, brachial, axillary, and subclavian veins. The subclavian vein converges with the internal jugular vein to form the brachiocephalic vein, which joins the contralateral brachiocephalic vein to form the superior vena cava. Bicuspid valves are present throughout the venous system to direct the flow of venous blood centrally.

Pathophysiology of Chronic Venous Disease *Varicose veins* are dilated, bulging, tortuous superficial veins, measuring at least 3 mm in diameter. The smaller and less tortuous reticular veins are dilated intradermal veins, which appear blue-green, measure 1–3 mm in diameter, and do not protrude from the skin surface. Telangiectasias, or spider veins, are small, dilated veins, <1 mm in diameter, located near the skin surface, and form blue, purple, or red linear, branching, or spider-web patterns.

Varicose veins can be categorized as primary or secondary. Primary varicose veins originate in the superficial system and result from defective structure and function of the valves of the saphenous veins, intrinsic weakness of the vein wall, and high intraluminal pressure. Approximately one-half of these patients have a family history of varicose veins. Other factors associated with primary varicose veins include aging, pregnancy, hormonal therapy, obesity, and prolonged standing. Secondary varicose veins result from venous hypertension, associated with deep-venous insufficiency or deep-venous obstruction, and incompetent perforating veins that cause enlargement of superficial veins. Arteriovenous fistulas also cause varicose veins in the affected limb.

Chronic venous insufficiency is a consequence of incompetent veins in which there is venous hypertension and extravasation of fluid and blood elements into the tissue of the limb. It may occur in patients with varicose veins and superficial venous disease, but more advanced manifestations are usually caused by disease in the deep veins. It also is categorized as primary or secondary. Primary venous insufficiency is a consequence of an intrinsic structural or functional abnormality in the vein wall or venous valves leading to valvular reflux. Secondary deep-venous insufficiency is caused by obstruction and/or valvular incompetence from previous deep-vein thrombosis (**Chap. 290**). Deep-venous insufficiency occurs following deep-vein thrombosis, as the delicate valve leaflets become thickened and contracted and can no longer prevent retrograde flow of blood and the vein itself becomes rigid and thick walled. Although most veins recanalize after an episode of thrombosis, the large proximal veins may remain occluded. Secondary incompetence develops in valves distal to the obstruction because high pressures distend the vein and separate the leaflets. Other causes of secondary deep-venous insufficiency include May-Thurner syndrome, where the left iliac vein is occluded or stenosed by extrinsic compression from the overlapping right common iliac artery; extrinsic compression from tumor or retroperitoneal fibrosis; arteriovenous fistulas resulting in increased venous pressure; congenital deep-vein agenesis or hypoplasia; and venous malformations as may occur in Klippel-Trénaunay and Parkes-Weber syndromes.

Clinical Presentation Patients with venous varicosities are often asymptomatic but still concerned about the cosmetic appearance of their legs. Superficial venous thrombosis may be a recurring problem, and rarely, a varicosity ruptures and bleeds. Symptoms in patients with varicose veins or venous insufficiency, when they occur, include a dull ache, throbbing or heaviness, or pressure sensation in the legs typically after prolonged standing; these symptoms usually are relieved with leg elevation. Additional symptoms may include cramping, burning, pruritus, leg swelling, and skin ulceration.

The legs are examined in both the supine and standing positions. Visual inspection and palpation of the legs in the standing position confirm the presence of varicose veins. The location and extent of the varicose veins should be noted. Chronic venous insufficiency is characterized by the development of edema or other skin manifestations. Edema, stasis dermatitis, and skin ulceration near the ankle may be present if there is superficial venous insufficiency and venous hypertension. Findings of deep-venous insufficiency include increased leg circumference, venous varicosities, edema, and skin changes. The edema, which is usually pitting, may be confined to the ankles, extend above the ankles to the knees, or involve the thighs in severe cases. Over time, the edema may become less pitting and more indurated, particularly with the secondary development of lymphatic dysfunction. Dermatologic findings associated with venous stasis include hyperpigmentation, erythema, eczema, lipodermatosclerosis, *atrophie blanche*,



FIGURE 293-1 Venous insufficiency with active venous ulcer near the medial malleolus. (Courtesy of Dr. Steven Dean, with permission.)

and a phlebectasia corona. Lipodermatosclerosis is the combination of induration, hemosiderin deposition, and inflammation, and typically occurs in the lower part of the leg just above the ankle. *Atrophie blanche* is a white patch of scar tissue, often with focal telangiectasias and a hyperpigmented border; it usually develops near the medial malleolus. A phlebectasia corona is a fan-shaped pattern of intradermal veins near the ankle or on the foot. Skin ulceration may occur near the medial and lateral malleoli. A venous ulcer is often shallow and characterized by an irregular border, a base of granulation tissue, and the presence of exudate (**Fig. 293-1**).

Bedside maneuvers can be used to distinguish primary varicose veins from secondary varicose veins caused by deep-venous insufficiency. With the contemporary use of venous ultrasound (see below), however, these maneuvers are employed infrequently. The Brodie-Trendelenburg test is used to determine whether varicose veins are secondary to deep-venous insufficiency. As the patient is lying supine, the leg is elevated and the veins allowed to empty. Then, a tourniquet is placed on the proximal part of the thigh and the patient is asked to stand. Filling of the varicose veins within 30 s indicates that the varicose veins are caused by deep-venous insufficiency and incompetent perforating veins. Primary varicose veins with superficial venous insufficiency are the likely diagnosis if venous refilling occurs promptly after tourniquet removal. The Perthes test assesses the possibility of deep-venous obstruction. A tourniquet is placed on the mid thigh after the patient has stood, and the varicose veins are filled. The patient is then instructed to walk for 5 min. A patent deep-venous system and competent perforating veins enable the superficial veins below the tourniquet to collapse. Deep-venous obstruction is likely to be present if the superficial veins distend further with walking.

Differential Diagnosis The duration of leg edema helps to distinguish chronic venous insufficiency from acute deep-vein thrombosis. Lymphedema, as discussed later in this chapter, is often confused with chronic venous insufficiency, and both may occur together when venous insufficiency impairs lymphatic function leading to phlebo-lymphedema. Other disorders that cause leg swelling should be considered and excluded when evaluating a patient with presumed venous insufficiency. Bilateral leg swelling occurs in patients with congestive heart failure, hypoalbuminemia secondary to nephrotic syndrome or severe hepatic disease, or myxedema caused by hypothyroidism or pretibial myxedema associated with Graves' disease, and with drugs such as dihydropyridine calcium channel blockers and thiazolidinediones. Unilateral causes of leg swelling also include ruptured leg muscles,

hematomas secondary to trauma, and popliteal cysts. Cellulitis may cause erythema and swelling of the affected limb. Leg ulcers may be caused by severe peripheral artery disease and chronic limb threatening ischemia; neuropathies, particularly those associated with diabetes; and less commonly, skin cancer, vasculitis, or rarely as a complication of hydroxyurea. The location and characteristics of venous ulcers help to differentiate these from other causes.

Classification of Chronic Venous Disease The CEAP (clinical, etiologic, anatomic, pathophysiologic) classification schema incorporates the range of symptoms and signs of chronic venous disease to characterize its severity. It also broadly categorizes the etiology as primary, secondary, or congenital; identifies the affected veins as superficial, deep, or perforating; and characterizes the pathophysiology as reflux, obstruction, both, or neither (Table 293-1).

Diagnostic Testing The principal diagnostic test to evaluate patients with chronic venous disease is venous duplex ultrasonography. A venous duplex ultrasound examination uses a combination of B-mode imaging and spectral Doppler to detect the presence of venous obstruction and venous reflux in superficial and deep veins. Color-assisted Doppler ultrasound is useful to visualize venous flow patterns. Obstruction may be diagnosed by the absence of flow, the presence of an echogenic thrombus within the vein, or failure of the vein to collapse when a compression maneuver is applied by the sonographer, the last implicating the presence of an intraluminal thrombus. Venous reflux is detected by prolonged reversal of venous flow direction during a Valsalva maneuver, particularly for the common femoral vein or

saphenofemoral junction, or after compression and release of a cuff placed on the limb distal to the area being interrogated.

Some vascular laboratories use air or strange gauge plethysmography to assess the severity of venous reflux and complement findings from the venous ultrasound examination. Venous volume and venous refilling time are measured when the legs are placed in a dependent position and after calf exercise to quantify the severity of venous reflux and the efficiency of the calf muscle pump to affect venous return.

Magnetic resonance, computed tomographic, and conventional venography are rarely required to determine the cause and plan treatment for chronic venous insufficiency unless there is suspicion for pathology that might warrant intervention. These modalities are used to identify obstruction or stenosis of the inferior vena cava and iliofemoral veins, as may occur in patients with previous proximal deep-vein thrombosis; occlusion of inferior vena cava filters; extrinsic compression from tumors; and May-Thurner syndrome.

TREATMENT

Chronic Venous Disease

SUPPORTIVE MEASURES

Varicose veins usually are treated with conservative measures. Symptoms often decrease when the legs are elevated periodically, prolonged standing is avoided, and elastic support hose are worn. External compression with elastic stockings, multilayer elastic wraps, stretch bandages, or inelastic garments provides a counterbalance to the hydrostatic pressure in the veins. Although compression garments may improve symptoms and are recommended in patients with healed or active venous ulceration, they are not curative and do not prevent progression of varicose veins. Graduated compression stockings with pressures of 20–30 mmHg are suitable for most patients with simple varicose veins, although higher pressures may be required for patients with varicose veins and manifestations of venous insufficiency such as edema and ulcers.

Patients with chronic venous insufficiency also should be advised to avoid prolonged standing or sitting; frequent leg elevation is helpful. Graded compression therapy consisting of stockings or multilayered compression bandages is the standard of care for advanced chronic venous insufficiency characterized by edema, skin changes, or venous ulcers defined as CEAP clinical class C3–C6. Graduated compression stockings of 30–40 mmHg are more effective than lesser grades for healing venous ulcers. The length of stocking depends on the distribution of edema. Calf-length stockings are tolerated better by most patients, particularly elderly patients; for patients with varicose veins or edema extending to the thigh, thigh-length stockings or panty hose should be considered. Exercise training, including leg muscle strengthening, may improve calf muscle pump function and antegrade venous flow, and reduce the severity of chronic venous insufficiency. Overweight and obese patients should be advised to lose weight via caloric restriction and exercise or consult an obesity specialist for more advanced therapies.

In addition to a compression bandage or stocking, patients with venous ulcers also may be treated with low-adherent absorbent dressings that take up exudates while maintaining a moist environment. Other types of dressings include hydrocolloid (an adhesive dressing composed of polymers such as carboxymethylcellulose that absorbs exudates by forming a gel), hydrogel (a nonabsorbent dressing comprising >80% water or glycerin that moisturizes wounds), foam (an absorbent dressing made with polymers such as polyurethane), and alginate (an absorbent, biodegradable dressing that is derived from seaweed), but there is little evidence that these are more effective than low-adherent absorbent dressings. The choice of specific dressing depends on the amount of drainage, presence of infection, and integrity of the skin surrounding the ulcer. Ulcers should be debrided of necrotic tissue. Antibiotics are not indicated unless the ulcer is infected. The multilayered compression bandage or graduated compression garment is then put over the dressing.

TABLE 293-1 CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) Classification

Clinical Classification

- C₀ No visible or palpable signs of venous disease
- C₁ Telangiectasias or reticular veins
- C₂ Varicose veins
 - C_{2r} Recurrent varicose veins
- C₃ Edema
- C₄ Changes in skin and subcutaneous secondary to CVD
 - C_{4a} Pigmentation or eczema
 - C_{4b} Lipodermatosclerosis or atrophie blanche
 - C_{4c} Corona phlebectatica
- C₅ Healed venous ulcer
- C₆ Active venous ulcer
 - C_{6r} Recurrent active venous ulcer

Etiologic Classification

- E_p Primary
- E_s Secondary
 - E_{si} Secondary – intravenous
 - E_{se} Secondary – extravenous
- E_c Congenital
- E_n No cause identified

Anatomic Classification

- A_s Superficial
- A_p Perforator
- A_d Deep
- A_n No venous anatomic location identified

Pathophysiologic Classification

- P_r Reflux
- P_o Obstruction
- P_{ro} Reflux and obstruction
- P_n No pathophysiology identified

Abbreviation: CVD, chronic venous disease.

Source: Data from F Lurie et al: J Vasc Surg 8:342, 2020.

There are no drugs approved by the U.S. Food and Drug Administration for the treatment of chronic venous insufficiency. Diuretics may reduce edema, but at the risk of volume depletion and compromise in renal function. Topical steroids may be used for a short period of time to treat inflammation associated with stasis dermatitis. Several herbal supplements, such as horse chestnut seed extract (aescin); ruscus extract; flavonoids, including diosmin, hesperidin, or the two combined as micronized purified flavonoid fraction; and French maritime pine bark extract, are touted to have venoconstrictive and anti-inflammatory properties. Several meta-analyses have suggested that ruscus extract and micronized purified flavonoid fraction reduce pain, leg heaviness, and/or sensation of swelling, and that micronized purified flavonoid fraction, and perhaps pentoxifylline, in conjunction with compression therapy facilitates venous ulcer healing; however, there remains insufficient evidence to recommend the general use of these substances in patients with chronic venous insufficiency.

INTERVENTIONAL AND SURGICAL THERAPIES

Ablative procedures, including endovenous thermal and nonthermal ablation, sclerotherapy, and surgery, are used to treat varicose veins in selected patients who have persistent symptoms, great saphenous vein incompetence, and complications of venous insufficiency including dermatitis, edema, and ulcers in order to treat symptoms, accelerate healing, and prevent recurrence. Ablative therapy may also be indicated for cosmetic reasons.

Endovenous thermal ablation procedures of the saphenous veins include endovenous laser and radiofrequency ablation. To ablate the great saphenous vein, a catheter is placed percutaneously and advanced from the level of the knee to just below the saphenofemoral junction via ultrasound guidance. Thermal energy is then delivered as the catheter is pulled back. The heat injures the endothelium and media and promotes thrombosis and fibrosis, resulting in venous occlusion. Average 1- and 5-year occlusion rates exceed 90% following endovenous laser therapy and are slightly less after radiofrequency ablation. Deep-vein thrombosis of the common femoral vein adjacent to the saphenofemoral junction is an uncommon but potential complication of endovenous thermal ablation. Other adverse effects of thermal ablation procedures include pain, paresthesias, bruising, hematoma, and hyperpigmentation.

Nonthermal ablation procedures of the saphenous veins include endovenous delivery of a cyanoacrylate tissue adhesive, which causes fibrosis, and mechanochemical ablation, which involves insertion of a rotating wire to injure the endothelium and infusion of a liquid sclerosant. One-year occlusion rates approximate or exceed 90%, respectively. Adverse effects of nonthermal ablation procedures include superficial thrombophlebitis, deep vein thrombosis, ecchymoses, hematomas, and hyperpigmentation.

Sclerotherapy involves the injection of a chemical into a vein to cause fibrosis and obstruction. Sclerosing agents approved by the U.S. Food and Drug Administration include sodium tetradecyl sulfate, polidocanol, sodium morrhuate, and glycerin. The sclerosing agent is administered as a liquid or mixed with air or CO_2/O_2 to create a foam. It may be used to treat the great saphenous vein, but most commonly sclerotherapy is used to treat the affected tributaries of the great saphenous vein or incompetent perforating veins either as a standalone procedure or concomitant or staged with ablative procedures of the truncal superficial veins. Following completion of the procedure, elastic bandages are applied, or 30–40 mmHg compression stockings are worn for 1–2 weeks. Average 1- and 5-year occlusion rates are 81 and 74%, respectively, following sclerotherapy. Complications are uncommon and include deep-vein thrombosis, hematomas, damage to adjacent saphenous or sural nerves, and infection. Anaphylaxis is a very rare but severe complication.

Surgical therapy usually involves ligation and stripping of the great and small saphenous veins. The procedure is performed under general anesthesia. Incisions are made at the groin and the upper

calf. The great saphenous vein is ligated below the saphenofemoral junction, and a wire is inserted into the great saphenous vein and advanced distally. The proximal part of the great saphenous vein is secured to the wire and retrieved, i.e., stripped, via the calf incision. Stripping of the great saphenous vein below the knee and stripping of the small saphenous vein usually are not performed because of the respective risks of saphenous and sural nerve injury. Complications of great saphenous vein ligation and stripping include deep-vein thrombosis, bleeding, hematoma, infection, and nerve injury. Recurrent varicose veins occur in up to 50% patients by 5 years, due to technical failures, deep-venous insufficiency, and incompetent perforating veins. Endovenous ablation techniques are generally favored over ligation and stripping.

Stab phlebectomy is another surgical treatment for varicose veins. A small incision is made alongside the varicose vein, and it is avulsed by means of a forceps or hook. This procedure may be performed in conjunction with saphenous vein ligation and stripping or thermal or nonthermal ablation. Subfascial endoscopic perforator surgery (SEPS) uses endoscopy to identify and occlude incompetent perforating veins. It has largely been replaced, however, by ablative techniques applied directly to the perforating veins and performed in a staged manner for persistent or recurrent symptoms after treatment for the truncal veins.

Endovascular interventions, surgical bypass, and reconstruction of the valves of the deep veins are performed when feasible to treat patients with advanced chronic venous insufficiency who have not responded to other therapies. Catheter-based interventions, usually involving placement of endovenous stents, may be considered to treat some patients with chronic occlusion or stenosis of the iliac veins. Technical success rates exceed 85% in most series, and long-term patency is achieved in ~75% of these patients. Iliocaval bypass, femoroiliac venous bypass, and femorofemoral crossover venous bypass are procedures used occasionally to treat iliofemoral vein occlusion; saphenopopliteal vein bypass can be used to treat chronic femoropopliteal vein obstruction. Long-term patency rates for venous bypass procedures generally exceed 60% and are associated with improvement in symptoms. Surgical reconstruction of the valves of the deep veins and valve transfer procedures rarely are used to treat valvular incompetence. Valvuloplasty involves tightening the valve by commissural apposition. With valve transfer procedures, a segment of vein with a competent valve, such as a brachial or axillary vein, or adjacent saphenous or deep femoral vein, is inserted as an interposition graft in the incompetent vein. Both valvuloplasty and vein transfer operations may result in ulcer healing in the majority of patients, although they are uncommonly performed and the success rates are somewhat better with valvuloplasty.

Lymphedema Lymphedema is a chronic condition caused by impaired transport of lymph and characterized by swelling of one or more limbs and occasionally the trunk and genitalia. Fluid accumulates in interstitial tissues when there is an imbalance between lymph production and lymph absorption, a process governed in large part by Starling forces. Deficiency, reflux, or obstruction of lymph vessels perturbs the ability of the lymphatic system to reabsorb proteins that had been filtered by blood vessels, and the tissue osmotic load promotes interstitial accumulation of water. Persistent lymphedema leads to inflammatory and immune responses characterized by infiltration of mononuclear cells, fibroblasts, and adipocytes, leading to adipose and collagen deposition in the skin and subcutaneous tissues.

Lymphatic Anatomy Lymphatic capillaries are blind-ended tubes formed by a single layer of endothelial cells. The absent or widely fenestrated basement membrane of lymphatic capillaries allows access to interstitial proteins and particles. Lymphatic capillaries merge to form microlymphatic precollector vessels, which contain few smooth muscle cells. The precollector vessels drain into collecting lymphatic vessels, which comprise endothelial cells, a basement membrane, smooth muscle, and bileaflet valves. The collecting lymphatic vessels

in turn merge to form larger lymphatic conduits. Analogous to venous anatomy, there are superficial and deep lymphatic vessels in the legs, which communicate at the popliteal and inguinal lymph nodes. Pelvic lymphatic vessels drain into the thoracic duct, which ascends from the abdomen to the thorax and connects with the left brachiocephalic vein. Superficial and deep lymphatic vessels of the arm communicate with axillary lymph nodes, and the efferent lymphatic vessels join lymphatic vessels from the head to form the right and left subclavian lymphatic trunks, which ultimately enter the right brachiocephalic vein and thoracic duct, respectively. Lymph is propelled centrally by the phasic contractile activity of lymphatic smooth muscle and facilitated by the contractions of contiguous skeletal muscle. The presence of lymphatic valves ensures unidirectional flow.

Etiology Lymphedema may be categorized as primary or secondary (Table 293-2). The prevalence of primary lymphedema is ~1.15

per 100,000 persons <20 years of age. Females are affected more frequently than males. Primary lymphedema may be caused by agenesis, hypoplasia, hyperplasia, or obstruction of the lymphatic vessels. There are three clinical subtypes: congenital lymphedema, which appears shortly after birth; lymphedema praecox, which has its onset at the time of puberty; and lymphedema tarda, which usually begins after age 35. Familial forms of congenital lymphedema (Milroy's disease) and lymphedema praecox (Meige's disease) may be inherited in an autosomal dominant manner with variable penetrance; autosomal or sex-linked recessive forms are less common. At least 19 genes are associated with inherited forms of lymphedema. Mutations in the *FLT4* gene expressing vascular endothelial growth factor receptor 3 (*VEGFR3*), which is a determinant of lymphangiogenesis, cause Milroy's disease; and a mutation of the gene encoding *VEGF-C*, a ligand for *VEGFR3*, may cause a Milroy's disease-like phenotype. A mutation of the *LSC1* gene is associated with the cholestasis-lymphedema syndrome. Mutations in the *FOXC2* gene, which encodes a transcription factor that interacts with a signaling pathway involved in the development of lymphatic vessels, cause the lymphedema-distichiasis syndrome, in which lymphedema praecox occurs in patients who also have a double row of eyelashes. A mutation of *SOX18*, a transcription factor upstream of lymphatic endothelial cell differentiation, has been described in patients with lymphedema, alopecia, and telangiectasias (hypotrichosis, lymphedema, telangiectasia syndrome). Mutations of the *CCBE1* gene, which enhances the lymphangiogenic effects of *VEGF-C*, cause Hennekam's lymphangiectasia-lymphedema syndrome, and *KIF11* gene mutations are associated with microcephaly-lymphedema syndrome. Mutations of the *GATA2* gene, which is involved in the development of lymphatic valves, cause lymphedema and a predisposition to acute myeloid leukemia. Patients with a chromosomal aneuploidy, such as Turner's syndrome, Klinefelter's syndrome, or trisomy 18, 13, or 21, may develop lymphedema. Syndromic vascular anomalies associated with lymphedema also include Klippel-Trénaunay syndrome and Parkes-Weber syndrome. Other disorders associated with lymphedema include Noonan's syndrome, yellow nail syndrome, intestinal lymphangiectasia syndrome, lymphangiomyomatosis, and neurofibromatosis type 1.

Secondary lymphedema is an acquired condition that results from damage to or obstruction of previously normal lymphatic channels. Recurrent episodes of bacterial lymphangitis, usually caused by streptococci, are a very common cause of lymphedema. The most common etiology of secondary lymphedema worldwide is lymphatic filariasis, affecting >120 million children and adults and causing lymphedema and elephantiasis in 14 million of these affected individuals (Chap. 240). Recurrent bacterial lymphangitis by *Streptococcus* may result in chronic lymphedema. Other infectious causes include lymphogranuloma venereum and tuberculosis. A common acquired cause of lymphedema in tropical countries is podoconiosis, which results from barefoot exposure and absorption of silicate particles in soil derived from volcanic rock. In developed countries, the most common secondary cause of lymphedema is surgical excision or irradiation of axillary and inguinal lymph nodes for treatment of cancers, such as breast, cervical, endometrial, and prostate cancer, sarcomas, and malignant melanoma. Lymphedema of the arm occurs in 13% of breast cancer patients after axillary node dissection and in 22% after both surgery and radiotherapy. Lymphedema of the leg affects ~15% of patients with cancer after inguinal lymph node dissection. Tumors, such as prostate cancer and lymphoma, also can infiltrate and obstruct lymphatic vessels. Chronic venous insufficiency is gaining recognition as a cause of lymphedema termed phlebolympedema. Less common causes include contact dermatitis, rheumatoid arthritis, pregnancy, and self-induced or factitious lymphedema after application of tourniquets.

Clinical Presentation Lymphedema is generally a painless condition, but patients may experience a chronic dull, heavy sensation in the leg, and most often, they are concerned about the appearance of the leg. Lymphedema of the lower extremity initially involves the foot and gradually progresses up the leg so that the entire limb becomes

TABLE 293-2 Causes of Lymphedema	
Primary	
Sporadic (no identified cause)	
Genetic disorders	
Milroy's disease (<i>VEGFR3</i> , <i>VEGF-C</i>)	
Meige's disease (gene mutation not established)	
Lymphedema-distichiasis syndrome (<i>FOXC2</i>)	
Cholestasis-lymphedema (<i>LSC1</i>)	
Hennekam's lymphangiectasia-lymphedema syndrome (<i>LCCBE1</i>)	
Emberger's syndrome-lymphedema and predisposition to AML (<i>GATA2</i>)	
Microcephaly-lymphedema syndrome (<i>KIF11</i>)	
Hypotrichosis-lymphedema-telangiectasia (<i>SOX18</i>)	
Chromosomal aneuploidies	
Turner's syndrome	
Klinefelter's syndrome	
Trisomy 13, 18, or 21	
Other disorders associated with primary lymphedema	
Noonan's syndrome	
Klippel-Trénaunay syndrome	
Parkes-Weber syndrome	
Yellow nail syndrome	
Intestinal lymphangiectasia syndrome	
Lymphangiomyomatosis	
Neurofibromatosis type 1	
Secondary	
Infection	
Bacterial lymphangitis (<i>Streptococcus pyogenes</i> , <i>Staphylococcus aureus</i>)	
Lymphogranuloma venereum (<i>Chlamydia trachomatis</i>)	
Filariasis (<i>Wucheria bancrofti</i> , <i>Brugia malayi</i> , <i>B. timori</i>)	
Tuberculosis	
Neoplastic infiltration of lymph nodes	
Lymphoma	
Prostate	
Others	
Surgery or irradiation of axillary or inguinal lymph nodes for treatment of cancer iatrogenic	
Lymphatic division (during peripheral bypass surgery, varicose vein surgery, or harvesting of saphenous veins)	
Miscellaneous	
Chronic venous insufficiency	
Contact dermatitis	
Podoconiosis	
Rheumatoid arthritis	
Pregnancy	
Factitious	



FIGURE 293-2 **A.** Lymphedema characterized by swelling of the leg, nonpitting edema, and squaring of the toes. (Courtesy of Dr. Marie Gerhard-Herman, with permission.) **B.** Advanced chronic stage of lymphedema illustrating the woody appearance of the leg with acanthosis and verrucous overgrowths. (Courtesy of Dr. Jeffrey Olin, with permission.)

edematous (Fig. 293-2). In the early stages, the edema is soft and pits easily with pressure. Over time, subcutaneous adipose tissue accumulates, the limb enlarges further and loses its normal contour, and the toes appear square. Thickening of the skin is detected by Stemmer’s sign, which is the inability to tent the skin at the base of the toes. *Peau d’orange* is a term used to describe dimpling of the skin, resembling that of an orange peel, caused by lymphedema. In the chronic stages, the edema no longer pits and the limb acquires a woody texture as the tissues become indurated and fibrotic. The International Society of Lymphology describes four clinical stages of lymphedema (Table 293-3).

Differential Diagnosis Lymphedema should be distinguished from other disorders that cause unilateral leg swelling, such as deep-vein thrombosis and chronic venous insufficiency. In the latter condition, the edema is softer, and there is often evidence of a stasis dermatitis, hyperpigmentation, and superficial venous varicosities, as described earlier. Other causes of leg swelling that resemble

TABLE 293-3 Stages of Lymphedema
Stage 0 (or Ia)
A latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist for months or years before overt edema occurs.
Stage I
Early accumulation of fluid relatively high in protein content that subsides with limb elevation. Pitting may occur. An increase in proliferating cells may also be seen.
Stage II
Limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Late in stage II, the limb may or may not pit as excess fat and fibrosis supervene.
Stage III
Lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

Source: Adapted from The 2013 Consensus Document of the International Society of Lymphology: Lymphology 46:1, 2013.

lymphedema are myxedema and lipedema. Lipedema usually occurs in women and is caused by accumulation of adipose tissue in the leg from the thigh to the ankle with sparing of the feet.

Diagnostic Testing Physical examination is usually sufficient to establish a diagnosis of lymphedema. The evaluation of patients with lymphedema should include diagnostic studies to clarify the cause. Abdominal and pelvic ultrasound and computed tomography (CT) can be used to detect obstructing lesions such as neoplasms. Magnetic resonance imaging (MRI) of the affected limb may reveal a honeycomb pattern characteristic of lymphedema in the epifascial compartment and identify enlarged lymphatic channels and lymph nodes. MRI also is useful to distinguish lymphedema from lipedema. Lymphoscintigraphy and lymphangiography are rarely indicated, but either can be used to confirm the diagnosis or differentiate primary from secondary lymphedema. Lymphoscintigraphy involves the injection of radioactively labeled technetium-containing colloid into the distal subcutaneous tissue of the affected extremity, which is imaged with a scintigraphic camera to visualize lymphatic vessels and lymph nodes. Findings indicative of primary lymphedema include absent or delayed filling of the lymphatic vessels or dermal back flow caused by lymphatic reflux. Findings of secondary lymphedema include dilated lymphatic vessels distal to an area of obstruction. In lymphangiography, iodinated radiocontrast material is injected into a distal lymphatic vessel that has been isolated and cannulated. In primary lymphedema, lymphatic channels are absent, hypoplastic, or ectatic. In secondary lymphedema, lymphatic channels often appear dilated beneath the level of obstruction. The complexities of lymphatic cannulation and the risk of lymphangitis associated with the contrast agent limit the utility of lymphangiography. Optical imaging with a near-infrared fluorescence dye enables quantitative imaging of peripheral superficial lymph flow and is useful in the operative setting.

TREATMENT
Lymphedema

Patients with lymphedema of the lower extremities must be instructed to take meticulous care of their feet and legs to prevent cellulitis and lymphangitis. Skin hygiene is important, and emollients can be used to prevent drying. Prophylactic antibiotics are often helpful, and fungal infection should be treated aggressively. Patients should be encouraged to participate in physical activity, as exercise may minimize symptoms and maintain functionality; frequent leg elevation can reduce the amount of edema. Psychosocial support is indicated to assist patients cope with anxiety or depression related to body image, self-esteem, functional disability, and fear of limb loss.

Physical therapy, including massage to facilitate lymphatic drainage, may be helpful. The type of massage, termed manual lymphatic drainage, is part of comprehensive decongestive physiotherapy for lymphedema and involves mild compression of the skin of the affected extremity to dilate the lymphatic channels and enhance lymphatic motility. Multilayered, compressive bandages are applied after each massage session to reduce recurrent edema. After optimal reduction in limb volume by decongestive physiotherapy, patients can be fitted with graduated compression hose or other adjustable compression garments. Sequential intermittent pneumatic compression devices can also be applied at home to facilitate reduction of the edema, improve quality of life, and reduce recurrent cellulitis. Diuretics are contraindicated and may cause depletion of intravascular volume and metabolic abnormalities. Failure to control limb edema may lead to recurrent infections, progressive trophic skin changes, and rarely a highly lethal complication of lymphangiosarcoma.

Liposuction in conjunction with decongestive physiotherapy may be considered to treat lymphedema, particularly postmastectomy

lymphedema. Other surgical interventions, including lymph node transfer, are rarely used and often not successful in ameliorating lymphedema. Microsurgical lymphaticovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system and may improve lymphatic transport and quality of life in secondary lymphedema. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility. Modification of surgical techniques to minimize impact upon the lymphatic system or enhance drainage with prophylactic lymphatic-venous shunts are being employed during operations that require lymph node dissection to reduce the risk of lymphedema.

Therapeutic lymphangiogenesis has intriguing potential as it has been studied in animal models of lymphedema. Overexpression of VEGF-C generates new lymphatic vessels and improves lymphedema in a murine model of primary lymphedema. The administration of recombinant VEGF-C or VEGF-D stimulated lymphatic growth in preclinical models of postsurgical lymphedema. There may be additional benefits when administered in conjunction with lymph node transfer. However, clinical trials in patients with lymphedema are still required to determine efficacy of gene transfer and cell-based therapies for lymphedema.

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294

Pulmonary Hypertension

Bradley A. Maron, Joseph Loscalzo

Pulmonary hypertension (PH) is a heterogeneous disease involving pathogenic remodeling of the pulmonary vasculature, which increases pulmonary artery pressure and pulmonary vascular resistance (PVR). The most common causes of PH are left heart or primary lung disease. Additionally, PH is observed in some patients as a later complication of luminal pulmonary embolism and may be observed variably in patients with various hematologic, myeloproliferative, and other systemic diseases. Pulmonary arterial hypertension (PAH) is an uncommon, but distinct, PH subtype characterized by the interplay between molecular and genetic events that cause an obliterative arteriopathy and symptoms of dyspnea, chest pain, and syncope. If left untreated, PH carries a high mortality rate, largely owing to decompensated right heart failure.

There have been significant advances in diagnosis, classification, and treatment of PH patients. For example, the mean pulmonary artery pressure (mPAP) used to diagnose PH has been lowered from ≥ 25 mmHg to >20 mmHg, and the PVR level used to identify patients with PAH and other forms of precapillary PH has been lowered from ≥ 3 to >2 Wood units (WU). These adjustments emphasize earlier disease detection, as a substantial delay in diagnosis of up to 2 years is common in PAH and has important implications for both quality of life and life span. Clinicians should be able to recognize the signs and symptoms of PH and complete a systematic evaluation in at-risk patients. In this way, prompt diagnosis, appropriate treatment, and optimized patient outcome are achievable.

PATHOBIOLOGY

Apoptosis resistance, cell proliferation, dysregulated metabolism, and increased oxidant stress involving pulmonary vascular cells, pericytes, and adventitial fibroblasts underlie the pathogenesis of PAH. These events lead to hypertrophic, fibrotic, and plexogenic remodeling of distal (small) pulmonary arterioles, which decreases vascular compliance and promotes in situ thrombosis (Fig. 294-1). The remodeling pattern also includes extracellular matrix expansion, which is rich in integrins, nonfibrillar collagens, fibronectin, and other tensile proteins that stiffen affected blood vessels further. A minority of patients appear to have a vasoconstriction-dominant phenotype, which, if present, requires a unique treatment strategy discussed in greater detail below. There is now greater understanding that in PAH, right ventricular dysfunction occurs due not only to increased right ventricular afterload but also as a consequence of depressed right ventricular sarcomere function from chronic inflammation or autoimmune mechanisms.

Genetic Drivers Several germline variants in genes that regulate fundamental cellular processes such as growth, proliferation, or phenotype switching are associated with incident PAH and follow a familial pattern. A variant in the gene encoding bone morphogenetic protein receptor-2 (*BMPR2*) is the most common cause of hereditary PAH, although penetrance is variable and may be as low as 20% in some populations. Sporadic mutations involving *BMPR2* are also reported in PAH patients. *BMPR2* is within the (super)family of transforming growth factor- β (TGF- β) receptors that transduce a wide range of cellular events via stimulation by activins, inhibins, and bone morphogenetic proteins (Fig. 294-2). Indeed, imbalance between proliferative and antiproliferative TGF- β receptor signaling in PAH has emerged as a bona fide therapeutic target based on clinical trials testing the effect of activin signal inhibitor therapy on outcome in PAH (see section on sotatercept).

The advance of genome-wide association studies has expanded the range of genetic drivers linked to pathogenic mechanisms underlying PAH, to include *TBX4* and *SOX17*, which regulate activation of fibroblast growth factor-10 and hepatocyte growth factor, respectively. Genetic predisposition to PH in the setting of left heart disease is unresolved, although single-gene polymorphisms that target actin

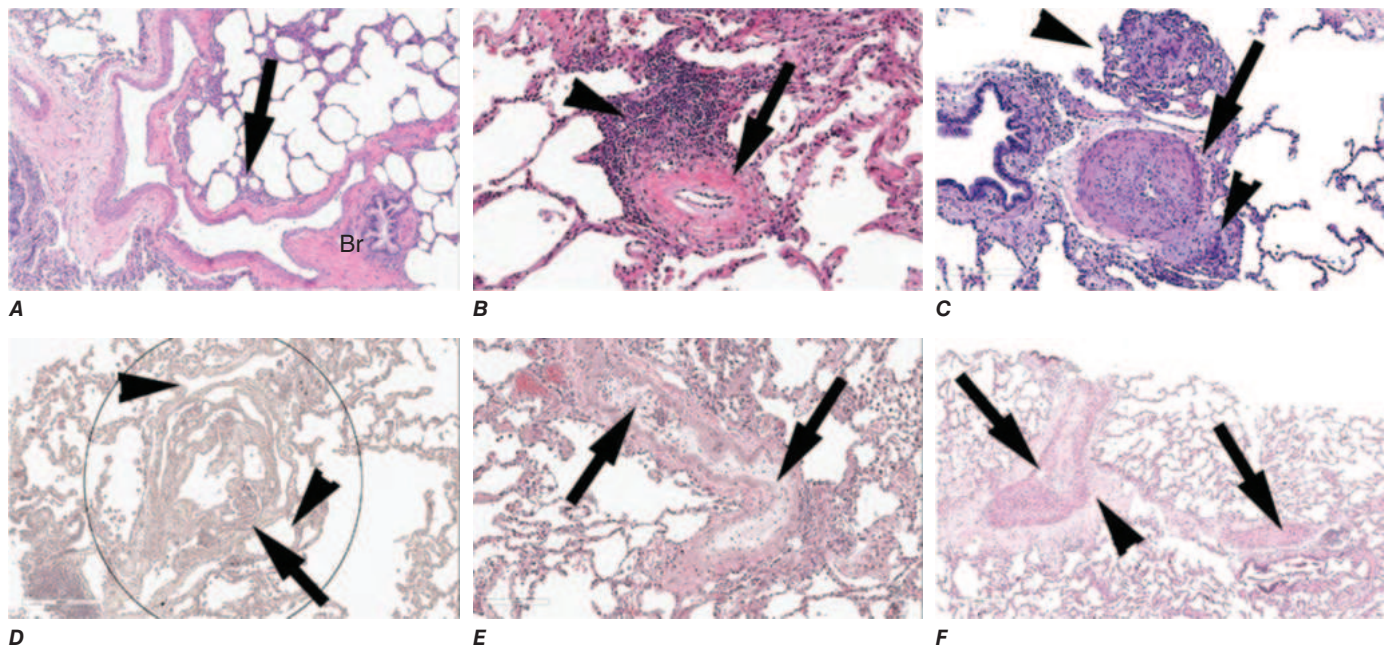


FIGURE 294-1 Panels on the left show examples of **plexogenic pulmonary arteriopathy**. Representative images of a normal lung (**A**) and examples of pulmonary vascular remodeling in pulmonary arterial hypertension (**B–E**), including idiopathic pulmonary arterial hypertension (**B–E**) and pulmonary venoocclusive disease (**F**), are shown. **A**. Normal pulmonary artery (arrow) adjacent to a terminal bronchiole (Br). **B**. Marked media and intima thickening of small vessels (arrow), partly surrounded by lymphoid cells, form a cluster reminiscent of a primary follicle (arrowhead). **C**. Idiopathic pulmonary hypertension lung with a markedly muscularized medium-sized pulmonary artery (arrow), which distally branches into a plexiform lesion (lower arrowhead) and an adjacent plexiform lesion (upper arrowhead). **D**. Complex vascular lesion (circle) with a combination of telangiectatic-like dilations of the pulmonary artery (arrowheads) and a plexiform lesion (arrow). **E**. Medium-sized pulmonary artery with complete lumen obliteration with a loose collagen, poorly cellular matrix (arrows). **F**. Interlobular septal, medium-sized vein (arrowhead) obliterated by loose connective tissue (arrows), likely the result of an organized thrombus, characteristic of venoocclusive disease. (These representative images were provided courtesy of Dr. Rubin Tudor. The samples were obtained through the evaluation of lungs collected by the Pulmonary Hypertension Breakthrough Initiative, with similar pulmonary vascular pathology spectrum as reported in reference E Stacher et al: Modern age pathology of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 186:261, 2012. Adapted with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved. Reproduced with permission from BA Maron et al: Pulmonary Arterial Hypertension: Diagnosis, Treatment, and Novel Advances. *Am J Respir Crit Care Med* 203:1472, 2021.)

binding, basement membrane, and major histocompatibility complex II proteins have been reported in lung tissue of affected patients. A variant in *EIF2AK4* is an established genetic risk factor for pulmonary venoocclusive disease with a recessive mode of transmission, although clinical expression among carriers is evident initially across a wide age range (10–60 years).

Epigenetics in PH The baseline DNA damage profile is increased in pulmonary artery endothelial cells and circulating blood mononuclear

cells from PAH patients. This finding implicates DNA itself as a target of injury and is accompanied by epigenetic disease mechanisms involving methylation and demethylation that include translocation methylcytosine dioxygenase 2 (*TET2*) and methyltransferase 3B (*DNMT3B*). The extent to which these events are transmissible across generations remains limited to experimental disease models. Nevertheless, bromo-domain-containing 4 and histone deacetylation inhibition, particularly for HDAC-1 and HDAC-5, are promising future PAH therapeutics. Long noncoding RNAs, which regulate epigenetic (among other)

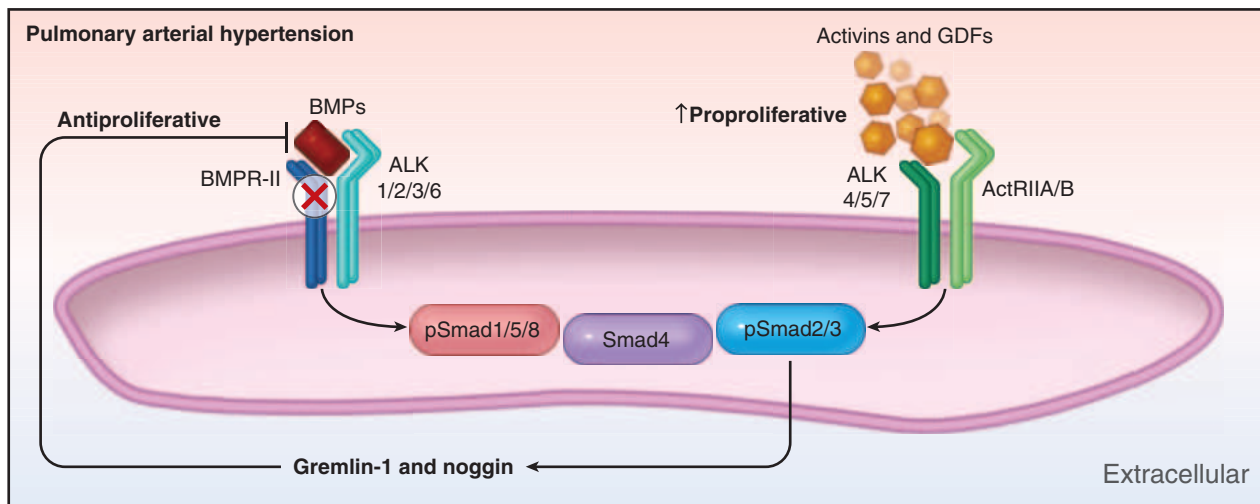


FIGURE 294-2 Pulmonary arterial hypertension is associated with dysregulation of the bone morphogenetic protein (BMP) receptor type II (BMPR-II)–Smad1/5/8 pathway in pulmonary vascular smooth muscle and endothelial cells, causing an imbalance between proliferative and antiproliferative signaling pathways. BMPR-II–Smad1/5/8 pathway downregulation leads to increased production of activin ligands, such as activin A, growth differentiation factor 8 (GDF8), and GDF11, which contributes to activin receptor type IIA (ActRIIA)–Smad2/3 pathway upregulation. Increased phosphorylated Smad (pSmad) 2/3 activity promotes expression of the endogenous BMP antagonists gremlin-1 and noggin. Gremlin-1 and noggin further reduce BMP–Smad1/5/8 signaling. The overall result is that antiproliferative signaling is reduced, shifting the balance toward proliferative activin–Smad2/3 signaling, which leads to pulmonary vascular remodeling. (Adapted from M Humbert et al: *N Engl J Med* 384:1204, 2021.)

processes that underpin hypertrophic vascular remodeling in PAH, include the tyrosine kinase receptor-inducing long noncoding RNA through its effects on p53/platelet-derived growth factor receptor β in lung pericytes. At present, hypoxia is the most well-studied epigenetic driver linked to PH, but a practical framework to predict disease onset through this mechanism in individual patients is unresolved.

Endothelial-Mesenchymal Transition Plexogenic and fibrotic pulmonary arterial remodeling in PAH is linked to cellular phenotype switching, particularly endothelial-mesenchymal transition (End-MT) for which specific markers are identified in ~6% of cells in explanted lungs from patients or at autopsy. Inflammation as well as hypoxia plus vascular endothelial growth factor receptor inhibition have been shown to increase End-MT, which in affected cells is characterized by migration, gain of smooth muscle actin fibers, and loss of cell-cell contacts. Interestingly, End-MT is related to a loss of BMPR2 expression, tying together a monogenic risk to a key endophenotype that drives PAH pathology.

Hypoxia, Metabolism, and Matrix Remodeling Abnormalities in multiple molecular pathways, genes, and cell types are associated with potentially modifying therapeutics, particularly those that focus on extracellular matrix remodeling (Fig. 294-3). The tyrosine kinase Janus kinase 2 (JAK2) is overactivated in PAH, which is inhibited by ruxolitinib to attenuate cellular proliferation and experimental PH. Hypoxia-inducible factor (HIF) signaling is a potentially modifiable disease-causing pathway, as treatment with the novel HIF-2 α inhibitor PT2567 improves hemodynamics and vascular remodeling in PAH.

Pulmonary artery smooth muscle cells isolated from PAH patients preferentially synthesize lactic acid in the presence of abundant molecular oxygen (Warburg effect). This metabolic change results in a proliferative cellular phenotype and has stimulated intense interest on metabolic modulating therapies. Dichloroacetate, which inhibits pyruvate dehydrogenase kinase to normalize voltage-gated K⁺ channels and promote pulmonary artery smooth muscle cell apoptosis, has been tested clinically with overall mixed results but a signal toward predicting treatment response by *SIRT3* and *UCP2* genotype. Nonetheless, numerous alternative metabolic targets show therapeutic promise, including SOD2, PPAR γ , and NFAT. Finally, there is greater interest in reverse remodeling pathways in PAH. For example, matrix metalloproteinase (MMP)-8 is protective against PAH by stabilizing mechanosensitive focal adhesion kinase–yes-associated protein/transcriptional coactivator with PDZ-binding motif (FAK–YAP/TAZ). This stabilization, in turn, suppresses extracellular matrix expansion and vascular fibrosis.

■ PATHOPHYSIOLOGY

In PAH, plexogenic and fibrotic remodeling of pulmonary arterioles impairs pulmonary arterial compliance and results in a progressive increase in total PVR. The resting PVR increases through the temporal progression of PAH, corresponding to a rise in mPAP. To preserve cardiac output (CO) in the face of elevated right ventricular afterload, right ventricular work must increase. A sustained (or progressive) increase in right ventricular work causes a shift in the efficiency of right ventricular systolic function by which maintaining pulmonary

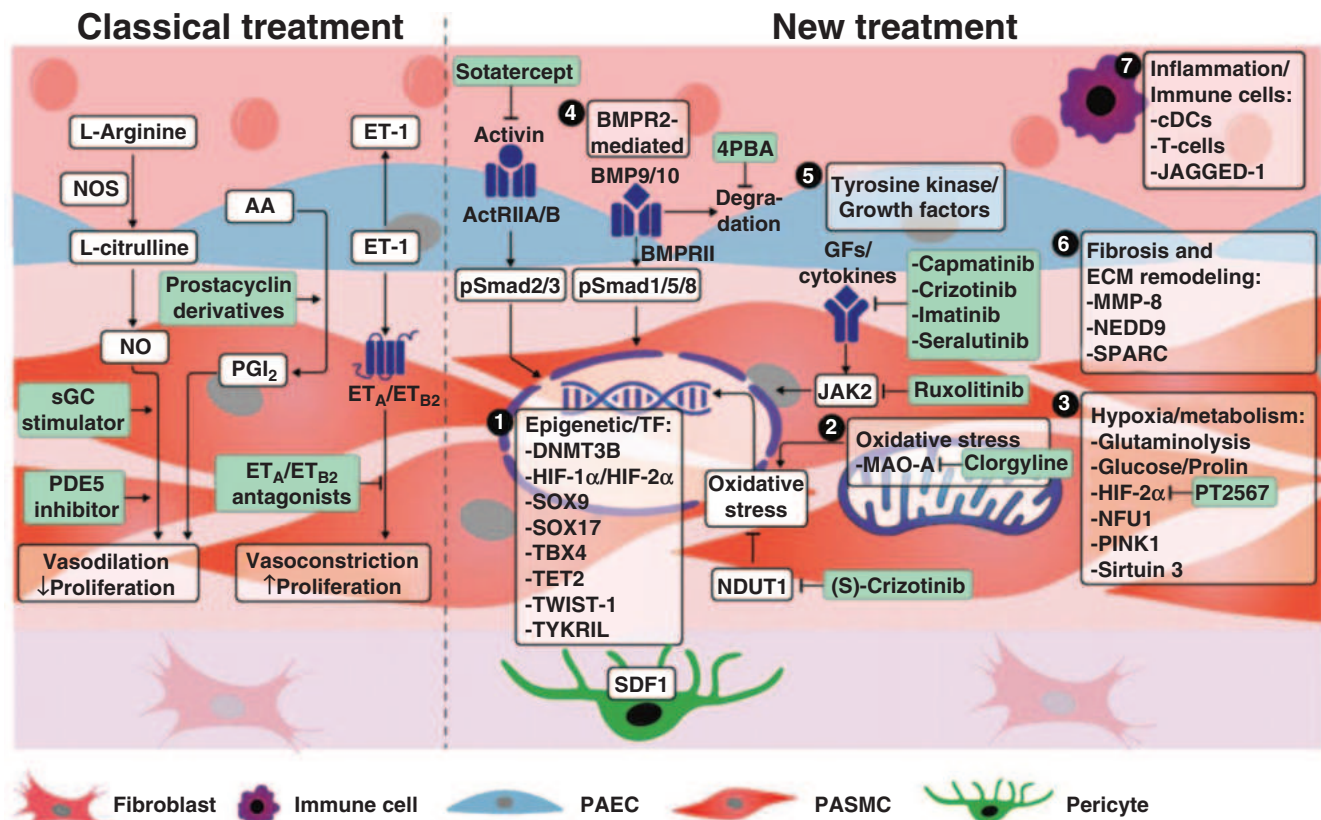


FIGURE 294-3 Modifiable pathobiological targets in pulmonary arterial hypertension. Current treatment approaches focus on endothelin, nitric oxide, and prostacyclin signaling. Novel treatment targets address (1) epigenetic mechanisms/transcriptional factors; (2) oxidative stress; (3) hypoxia and metabolic signaling; (4) BMPR2-mediated signaling; (5) tyrosine kinase and growth factor signaling; (6) fibrosis and extracellular matrix remodeling; and (7) inflammation and immune cell infiltration. 4PBA, 4-phenylbutyric acid; AA, arachidonic acid; ActRII, activin receptor type II; BMP, bone morphogenetic protein; BMPR2, bone morphogenetic protein receptor type 2; cDC, conventional dendritic cell; DNMT3B, DNA methyltransferase 3 b; ET, endothelin; GDFs, growth and differentiation factors; HIF = hypoxia-inducible factor; JAGGED-1, jagged canonical Notch ligand 1; JAK, Janus kinase; MAO-A, monoamine oxidase A; MMP, matrix metalloproteinase; NDUT1, nudix hydrolase 1; NEDD9, neural precursor cell-expressed developmentally downregulated protein 9; NFU1, NFU1 iron-sulfur cluster scaffold; NO, nitric oxide; NOS, nitric oxide synthase; PAEC, pulmonary artery endothelial cell; PASMC, pulmonary arterial smooth muscle cell; PDE5, phosphodiesterase 5; PGI₂, prostacyclin; PINK1, phosphatase and tensin homolog-induced kinase 1; SDF1, stromal cell-derived factor 1; sGC, soluble guanylate cyclase; SOX9, SRY-box transcription factor 9; SOX17, SRY-box transcription factor 17; SPARC, secreted protein acidic and rich in cysteine; TBX4, T-box transcription factor 4; TET2, Tet methylcytosine dioxygenase 2; TWIST1, Twist family BHLH transcription factor 1; TYKRIL, tyrosine kinase receptor-inducing long noncoding RNA. (Reproduced with permission from SJ Johnson et al: *Am J Respir Crit Care Med* 208:528, 2023.)

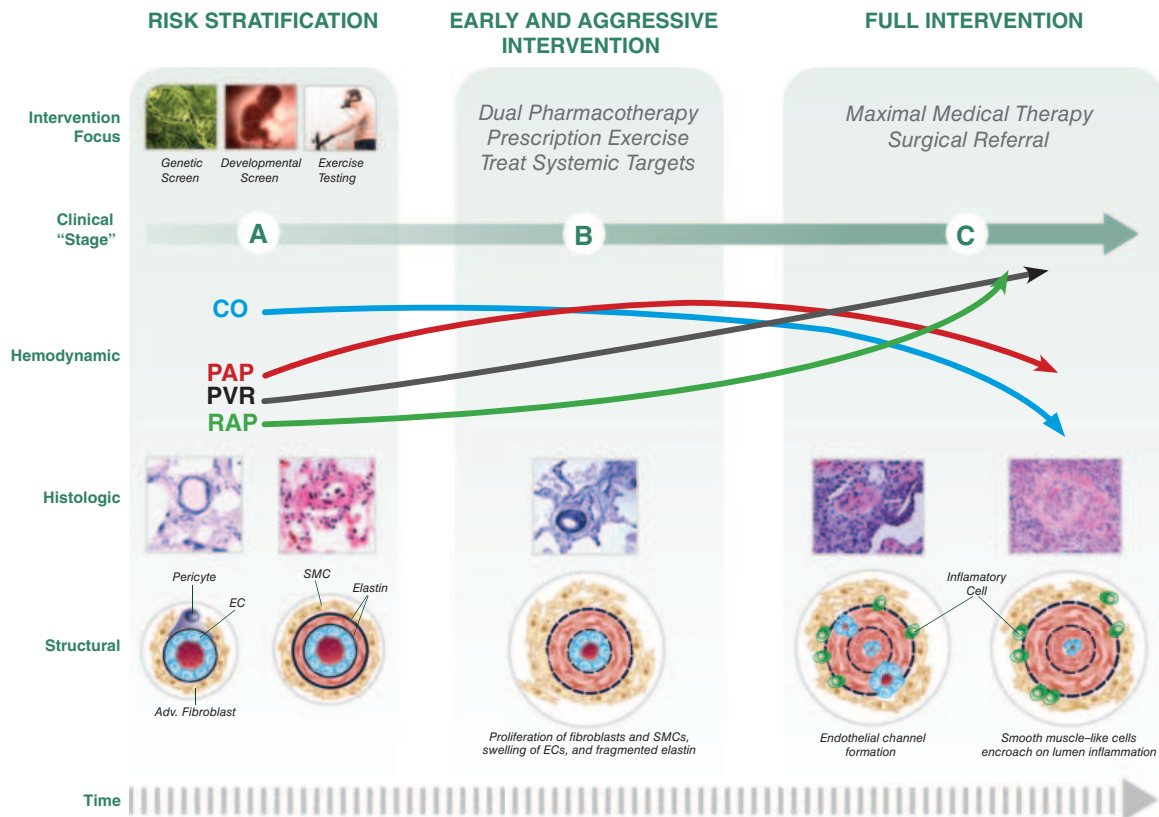


FIGURE 294-4 An integrated overview of pulmonary arterial hypertension (PAH). In PAH, initial changes in the histopathophenotype of distal pulmonary arterioles precede significant changes in hemodynamics or the development of symptoms in most patients (clinical stage A). As vascular remodeling progresses, there is an increase in pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP), and right atrial pressure (RAP). In clinical stage B, symptoms are evident and, when diagnosed, prompt early, aggressive treatment. Effacement of pulmonary arterioles results in severely increased PVR that promotes right heart failure, defined by a decrease in cardiac output (CO) and PAP. Patients in clinical stage C have severe symptoms and require full therapeutic intervention. Identifying clinical stage A patients remains challenging, although genetic risk factors or symptoms with exercise may be informative. EC, endothelial cell; SMC, smooth muscle cell. (Reproduced with permission from Maron BA, Abman SH: Focusing on Developmental Origins and Disease Inception for the Prevention of Pulmonary Hypertension. *Am J Respir Crit Care Med* 195:292, 2017.)

circulatory pressure depletes myocardial energy. These changes occur at the expense of energy normally reserved to maintain optimal blood perfusion through the alveolar-capillary interface for blood oxygenation, a process termed right ventricular–pulmonary arterial uncoupling. In end-stage PAH, the CO declines, leading to a decrease in mPAP (Fig. 294-4), with extrapulmonary vascular manifestations. These include overactivation of neurohumoral signaling, renal failure, abnormal episcleral vessels (seen in patients with hereditary PAH due to *BMPR2* mutation), and hyper- or hypothyroidism. Volitional muscle atrophy in PAH is associated with reduced muscle strength, type I fiber switching to fatigable type II fibers, and decreased capillary density. This myopathy affects respiratory function, as well, including impairment of maximal inspiratory and expiratory pressure. Overall, sarcopenia in PAH with right ventricular heart failure is likely multifactorial, driven by deconditioning and alternative pathophysiological mechanisms linked to impaired cardiac output (i.e., neurohumoral signaling) and possibly through the ectopic effects of molecular intermediaries such as miR-136 downregulation (Fig. 294-5).

DIAGNOSIS

The diagnosis of PH can be missed without a reasonable index of suspicion. Indeed, findings from clinical registries suggest that PH is often overlooked, even among patients with numerous risk factors. This shortcoming may be because PH symptoms are nonspecific, insidious, and overlap considerably with many common conditions, such as asthma, heart failure with preserved ejection fraction, and deconditioning. Additionally, there is a misconception that in patients with comorbid cardiopulmonary conditions (e.g., interstitial lung disease, mitral valve disease), PH is merely an extension of the underlying disease rather than a specific clinical entity.

Most patients will present with dyspnea and/or fatigue, whereas edema, chest pain, presyncope, and syncope are less common and associated with more advanced disease. In early phases of PAH, the physical examination is often unrevealing. As the disease progresses, there may be evidence of right ventricular failure with elevated jugular venous pressure, lower extremity edema, and ascites. Additionally, the cardiovascular examination may reveal an accentuated P_2 component of the second heart sound, a right-sided S_3 or S_4 , and a holosystolic tricuspid regurgitant murmur. It is also important to seek signs of the diseases that are commonly concurrent with PH: clubbing may be seen in some chronic lung diseases, sclerodactyly and telangiectasia may signify scleroderma (or the limited cutaneous form, CREST [calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia]), and crackles on examination of the lungs and systemic hypertension may be clues to left-sided systolic or diastolic heart failure.

Overview of the Diagnostic Clinical Evaluation Once clinical suspicion is raised, a systematic approach to diagnosis and assessment is essential. In advanced disease, electrocardiography may show right ventricular hypertrophy or strain, and enlargement of pulmonary arteries and obliteration of the retrosternal space are often observed on chest roentgenography (Fig. 294-6). In turn, echocardiography with agitated saline (bubble) study is the most important initial screening test. Elevated estimated pulmonary artery systolic pressure (>35 mmHg), notched waveform on continuous wave Doppler interrogation of the right ventricular outflow tract, or a hypertrophied or dilated right ventricle supports the diagnosis of PH. Important additional information can be gleaned about specific etiologies of PH, such as valvular disease, left ventricular systolic

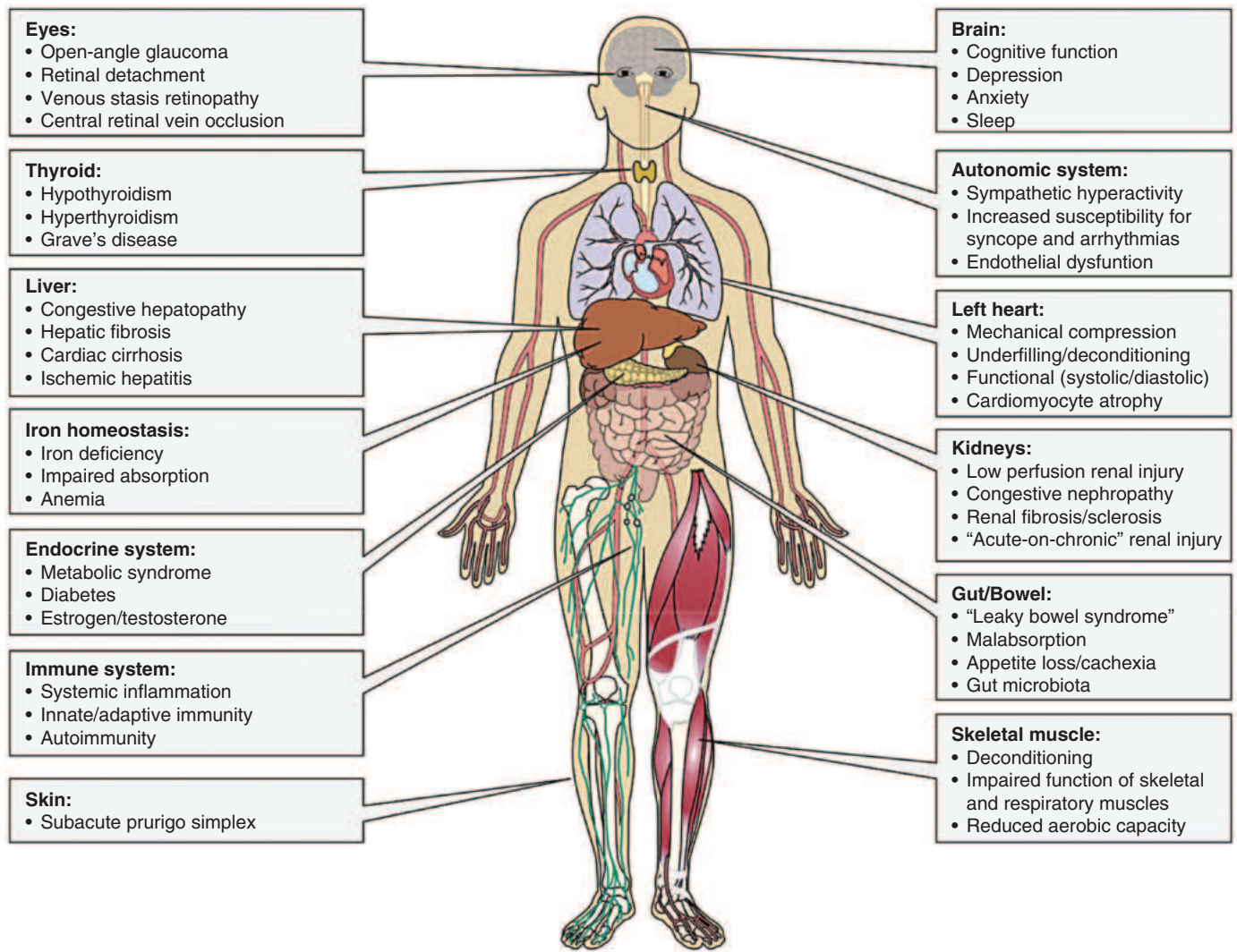


FIGURE 294-5 Systemic manifestations of right heart failure. (Reproduced with permission from S Rosenkranz et al: *Systemic consequences of pulmonary hypertension and right-sided heart failure. Circulation* 141:67, 2020.)

dysfunction, left atrial enlargement, and intracardiac shunt. In addition, hypertrophic cardiomyopathy (HCM), amyloid cardiomyopathy, and sarcoid cardiomyopathy, which are specific forms of left heart disease that predispose to PH, are linked to disease-specific approaches to treatment.

A high-quality echocardiogram that is absolutely normal may obviate the need for further PH evaluation. However, this is distinct from an echocardiogram in which tricuspid regurgitation is not detected. In this scenario, the information required to estimate pulmonary artery pressure is lacking, and PH is observed in one-third of such patients. Patients with evidence of PH on echocardiography or in whom unexplained dyspnea or hypoxemia is evident despite an unremarkable echocardiogram often require further assessment.

Additional tests focusing on functional capacity are useful for quantifying disease burden, such as a 6-minute walk distance (6-MWD) assessment, which also aids in assessing prognosis. Cardiopulmonary exercise testing (CPET) may differentiate between cardiac and pulmonary limitations to exercise thereby providing pathophysiologic insights on the cause of dyspnea. Peak volume of oxygen consumption ($\dot{V}O_2$), which is an integrated parameter of cardiopulmonary fitness, is prognostic in PH patients when <15 mL/kg/min. However, low $\dot{V}O_2$ is an important clinical finding across the spectrum of heart-lung disease and, thus, is not diagnostic of PH per se. In patients with a normal CPET, further invasive testing is often unnecessary. One exception to this approach is in patients with reassuring CPET results but in whom a significant decrease in exercise tolerance from baseline is nonetheless reported, often observed in elite athletes or highly conditioned individuals with early-stage PH or subacute pulmonary embolism.

Invasive hemodynamic monitoring with right heart catheterization (RHC) is the gold standard for PH diagnosis and severity assessment. Interpretation of RHC data, however, is often optimized by information from diagnostic tests that support and frame the clinical context of pulmonary vascular disease.

Stepwise Approach to Diagnosing PH One common PH diagnostic strategy is outlined in [Figure 294-7](#); however, the approach should be individualized in practice according to a particular patient's clinical and risk factor profile. For example, patients with a strong history of inhaled tobacco use may benefit from prioritizing diagnostic tests assessing pulmonary function and the lung parenchyma, whereas a myocardial ischemia evaluation should be considered early in the evaluation of patients with left-sided cardiomyopathy.

PULMONARY FUNCTION AND LUNG IMAGING Pulmonary function testing results may suggest restrictive or obstructive lung diseases as the cause of dyspnea or PH. In PAH, an isolated reduction in diffusing capacity of the lungs for carbon monoxide (DL_{CO}) is a classic finding. High-resolution computed tomography (CT) provides useful information, particularly enlargement of the main pulmonary artery, right ventricle, and atria, as well as peripheral pruning of small vessels; however, high-resolution CT may also reveal signs of venous congestion, including centrilobular ground glass infiltrate and thickened septa. In the absence of left heart disease, these findings suggest pulmonary venous disease, a rare cause of PAH that can be quite challenging to diagnose. CT is also critical for distinguishing comorbid interstitial lung disease, emphysema, or overlap syndromes that include fibrosis and obstructive pulmonary disease.

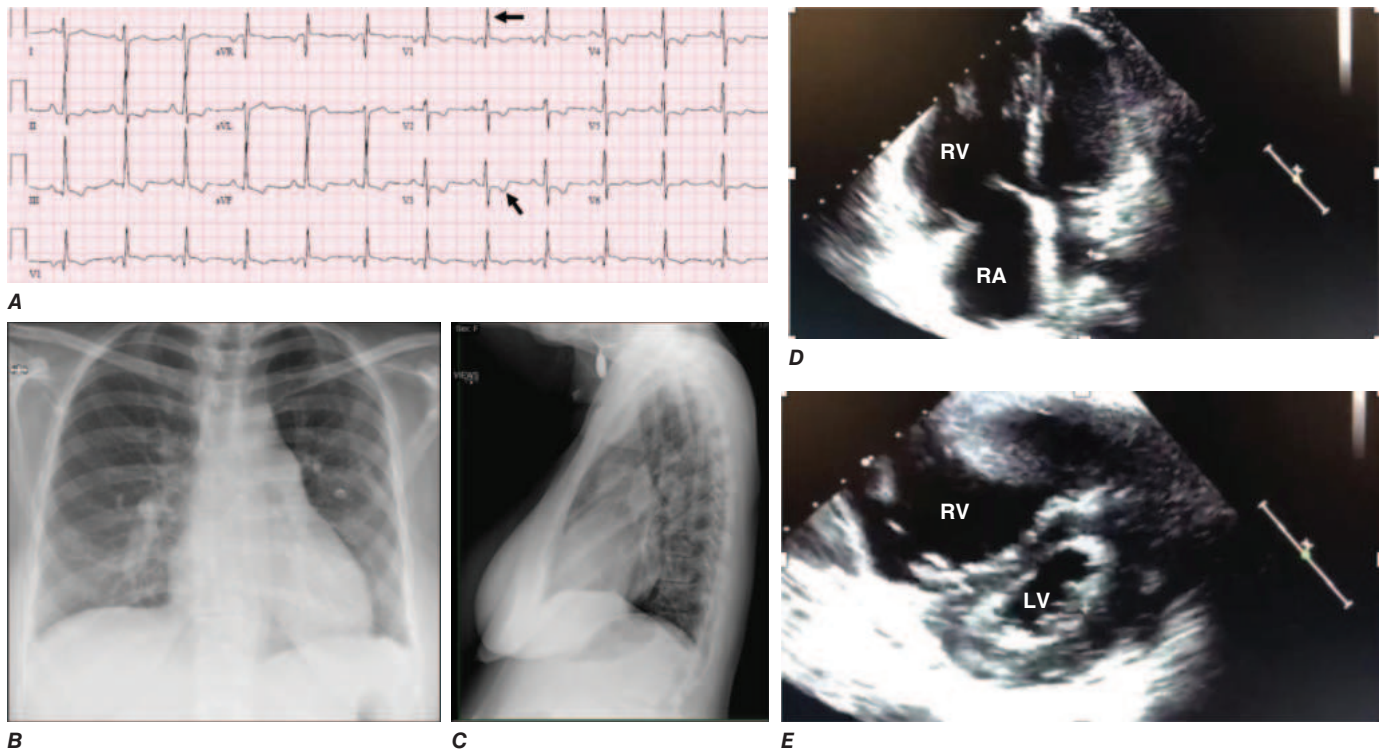


FIGURE 294-6 Electrocardiography, chest roentgenography, and two-dimensional echocardiography in advanced pulmonary arterial hypertension. **A.** Standard 12-lead electrocardiogram shows peaked R waves in lead V_1 and ST-segment depression in leads V_2 – V_4 , suggestive of right ventricular hypertrophy with strain (arrows). **B, C.** Anterior-posterior and lateral chest roentgenogram demonstrating enlargement of central pulmonary arteries and obliteration of the retrosternal space, indicative of right ventricular hypertrophy. **D, E.** Apical four-chamber and two-chamber short axis views acquired by transthoracic echocardiography demonstrate right ventricular (RV) and right atrial (RA) enlargement, as well as interventricular septal flattening in diastole consistent with pressure overload. LV, left ventricle.

SLEEP STUDIES Nocturnal desaturation is a common finding in PH, even in the absence of sleep-disordered breathing. Thus, all patients should undergo nocturnal oximetry screening, regardless of whether classic symptoms of obstructive sleep apnea or obesity-hypoventilation syndrome are present.

ASSESSMENT OF PULMONARY ARTERIAL THROMBOSIS Patients with prior luminal pulmonary embolism are at increased risk for chronic

thromboembolic pulmonary hypertension (CTEPH), which is a specific PH subtype characterized by vascular fibrosis and arterial microthrombus. Although CTEPH is curable in many patients by surgical endarterectomy, it is also widely underdiagnosed. Ventilation-perfusion (V/Q) scanning is still the primary test used to screen and diagnose CTEPH, which should be considered in any patient with PH of unclear etiology. Nonetheless, CT angiography is increasingly used in clinical

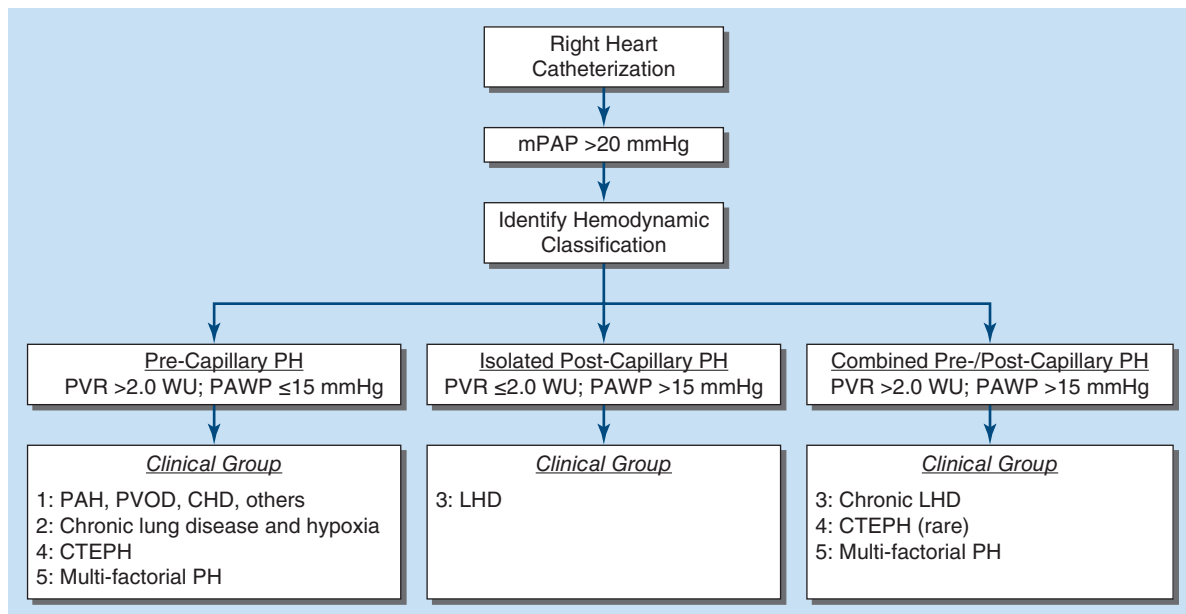


FIGURE 294-7 Integrating the cardiopulmonary hemodynamic and clinical profile of patients with pulmonary hypertension (PH). Diagnosing PH is achieved by right heart catheterization and requires a mean pulmonary artery pressure (mPAP) >20 mmHg. Patients are then classified by hemodynamic category, which together with the clinical profile and other supporting data (e.g., chest imaging, serology, genetic testing) is used to determine the PH clinical group. Certain clinical groups are incompatible with hemodynamic classifications; for example, pulmonary arterial hypertension (PAH) cannot be diagnosed in patients with isolated postcapillary or combined pre-/postcapillary PH hemodynamics. CHD, congenital heart disease; CTEPH, chronic thromboembolic PH; LHD, left heart disease; PAWP, pulmonary artery wedge pressure; PVOD, pulmonary venoocclusive disease; PVR, pulmonary vascular resistance. (Reproduced with permission from BA Maron et al: *Cardiopulmonary hemodynamics in pulmonary hypertension and heart failure: JACC Review Topic of the Week*. J Am Coll Cardiol 76:2671, 2020.)

practice to manage CTEPH especially for staging anatomic thromboembolic burden, which may be ultimately necessary to determine operative candidacy. The definitive diagnostic procedure is digital subtraction pulmonary angiography since contrast enhancement in this study provides detailed information on webbing, stricture, and vascular tapering patterns pathognomonic for CTEPH.

SEROLOGY Laboratory data that are important for screening include a human immunodeficiency virus (HIV) test when clinically indicated. In addition, all patients should have antinuclear antibodies, rheumatoid factor, and anti-Scl-70 antibodies assessed to screen for the most common rheumatologic diseases associated with PH. Liver function and hepatitis serology tests are important to screen for underlying liver disease. Methamphetamine use is recognized increasingly as a cause of PAH, and screening should be considered in patients from endemic regions or in whom the cause of PAH is not otherwise established. Finally, brain natriuretic peptide (BNP) and the N-terminus of its propeptide (NT-proBNP) correlate with right ventricular dysfunction, hemodynamic severity, and functional status in PAH. Medical therapy also lowers NT-proBNP levels in PAH, and therefore, this test may be used as a biomarker for assessing treatment response in clinical practice once a baseline level is established.

INVASIVE CARDIOPULMONARY HEMODYNAMICS The RHC remains the gold standard test to both establish the diagnosis of PH and guide selection of appropriate medical therapy. The hemodynamic criteria for diagnosing PH requires, first, an mPAP >20 mmHg. Precapillary and postcapillary PH are then distinguished by virtue of a pulmonary artery wedge pressure (PAWP) (or left ventricular end-diastolic pressure [LVEDP]) ≤15 mmHg or >15 mmHg, respectively. Isolated precapillary PH also requires a PVR >2.0 WU, whereas isolated postcapillary PH is defined by PVR ≤2.0 WU. Increasingly, combined pre- and postcapillary PH is recognized, defined by elevated mPAP >20 mmHg, PVR >2.0 WU, and PAWP >15 mmHg (Fig. 294-7).

These hemodynamic profiles inform PH clinical categorization. For example, isolated precapillary PH is most often due to primary lung disease, PAH, or CTEPH. Isolated postcapillary PH occurs in patients with mitral valvular disease, left ventricular systolic dysfunction, heart failure with preserved ejection fraction, HCM, and amyloid cardiomyopathy. The same etiologies for isolated postcapillary PH also underlie combined pre- and postcapillary PH. When present, this indicates that chronic vascular congestion due to left atrial hypertension has resulted in substantial pulmonary vascular remodeling, although the precise mechanisms that transition patients from isolated postcapillary PH to combined pre-/postcapillary PH are not known. Patients with left heart disease risk factors who are diuresed aggressively prior to RHC may appear to have an isolated precapillary PH profile, tempting a diagnosis of PAH. However, these patients require specific consideration given the potential effects of diuresis on masking the true underlying PH hemodynamic classification.

Vasoreactivity testing should be reserved for patients with idiopathic or hereditary PAH. Vasodilators with a short duration of action, such as inhaled nitric oxide (NO) or inhaled epoprostenol, are preferred for testing. A decrease in mPAP by ≥10 mmHg to an absolute level ≤40 mmHg without a decrease in CO is defined as a positive pulmonary vasodilator response, and such responders are considered for long-term treatment with calcium channel blockers. Less than 5% of patients are deemed vasoreactive, although prognosis among these patients is particularly favorable.

■ PULMONARY HYPERTENSION CLASSIFICATION

The current classification system, last revised in 2018 during the Sixth World Symposium on Pulmonary Hypertension (WSPH), recognizes five PH categories listed here sequentially as groups 1–5: PAH; PH due to left heart disease; PH due to chronic lung disease or sleep-disordered breathing; CTEPH; and a group of miscellaneous diseases that rarely (or inconsistently) cause PH (Table 294-1).

Pulmonary Arterial Hypertension WSPH group 1 PH, or PAH, involves marked pulmonary arterial precapillary remodeling,

TABLE 294-1 World Symposium on Pulmonary Hypertension Clinical Classification

GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
 - 1.1.1 Non-responders at vasoreactivity testing
 - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable^a
- 1.3 Associated with drugs and toxins^a
- 1.4 Associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

GROUP 2 PH associated with left heart disease

- 2.1 Heart failure:
 - 2.1.1 with preserved ejection fraction
 - 2.1.2 with reduced or mildly reduced ejection fraction^b
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

GROUP 3 PH associated with lung diseases and/or hypoxia

- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

GROUP 4 PH associated with pulmonary artery obstructions

- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions^c

GROUP 5 PH with unclear and/or multifactorial mechanisms

- 5.1 Hematological disorders^d
- 5.2 Systemic disorders^e
- 5.3 Metabolic disorders^f
- 5.4 Chronic renal failure with or without hemodialysis
- 5.5 Pulmonary tumor thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

Note: Patients with heritable PAH or PAH associated with drugs and toxins might be acute responders. Left ventricular ejection fraction for HF with reduced ejection fraction: ≤40%; for HF with mildly reduced ejection fraction: 41–49%. Other causes of pulmonary artery obstructions include: sarcomas (high or intermediate grade or angiosarcoma), other malignant tumors (e.g., renal carcinoma, uterine carcinoma, germ-cell tumors of the testis), non-malignant tumors (e.g., inherited and acquired chronic hemolytic anemia and chronic myeloproliferative disorders, sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1, glycogen storage diseases and Gaucher disease.)

Abbreviations: HF, heart failure; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

Source: Reproduced with permission of the © ERS 2024: Eur Resp J 61:2200879, 2023; DOI:10.1183/13993003.00879-2022.

including intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion, and classic plexiform lesions (described in detail above in the Pathobiology section). The hemodynamic criteria for PAH are sustained elevation in resting mPAP >20 mmHg, PVR >2.0 WU, and PAWP or LVEDP of ≤15 mmHg based on RHC. Idiopathic PAH (IPAH) is a progressive disease that leads to right heart failure and early mortality. From the original National Institutes of Health registry on IPAH in 1987, the average age at diagnosis was 36 years, with only 9% of patients with IPAH over the age of 60. However, contemporary data now inclusive of numerous international registries suggest a different clinical profile. The mean age of PAH patients is reported to be 54–68 years old across studies. This reflects, in part, rising awareness

of this disease in the elderly. The prevalence of IPAH favors women to men by ~3.1-fold; however, the hemodynamics at diagnosis are more severe, and the prognosis is less favorable in men compared to women. Patients with hereditary PAH from a *BMPR2* mutation tend to be younger at diagnosis with more severe cardiopulmonary hemodynamics and are associated with comparatively greater clinical risk compared to IPAH. The rate of conversion to PAH among carriers without clinical evidence of disease is ~2.3% per year.

Diseases Associated with PAH Other forms of PAH that deserve specific consideration are those associated with congenital heart disease with intracardiac shunt, connective tissue disease, portal hypertension, and HIV.

CONGENITAL HEART DISEASE PAH in the setting of congenital heart disease is important to recognize since surgical correction may be indicated and when successful is associated with favorable prognosis. This is particularly salient today, as more congenital heart disease patients live to adulthood and populate general medical practices. Still, referral to adult congenital heart disease centers should be considered for patients with suspected PAH, which in this population is subclassified into four groups: Eisenmenger's syndrome, systemic-to-pulmonary shunts, coincidental or small defects causing shunts, and postoperative/closed defects causing shunts. Surgical repair of congenital anatomic lesions may be indicated prior to elevation in PVR >3.0 WU to avoid the development of Eisenmenger's syndrome, a pathophysiologic consequence of progressive pulmonary vascular remodeling due to a large-volume left-to-right shunt that is associated with cyanosis, hyperviscosity, weakness, and shortened life span. Indeed, the effect of changing the PVR threshold to define precapillary PH from 3.0 to 2.0 WU on the timing of shunt repair is an evolving concept.

CONNECTIVE TISSUE DISEASE Patients with connective tissue disease-associated PAH are encountered relatively commonly in clinical practice. Although case series link rheumatoid arthritis and systemic lupus erythematosus with pulmonary vascular disease, the predominant clinical phenotype is systemic sclerosis-associated PAH. It is important to distinguish patients with limited cutaneous scleroderma from those with diffuse scleroderma because PH in the former is likely PAH and PH in the latter often occurs in the setting of interstitial lung disease. Although the average age of scleroderma onset is between 30 and 50 years old, patients who eventually develop scleroderma-associated PAH tend to be older at the time of scleroderma diagnosis. The development of PAH in scleroderma is particularly worrisome prognostically, although implementation of modern therapies improves outcome. Overlap between pulmonary circulatory and interstitial lung disease is encountered commonly in clinical practice. It is tempting to focus on the hemodynamic derangement of these patients as a focal point of clinical care, although the efficacy of implementing PAH-specific treatment to these overlap syndrome patients is unproven.

PORTOPULMONARY HYPERTENSION Among patients with established portal hypertension, 2–10% develop portopulmonary hypertension independent of the cause of liver disease. Furthermore, portopulmonary hypertension is observed in patients with nonhepatic etiologies of portal hypertension. A hyperdynamic circulatory state is common, as in most patients with advanced liver disease; however, the same pulmonary vascular remodeling observed in other forms of PAH is seen in the pulmonary vascular bed in portopulmonary hypertension. It is important to distinguish this process from hepatopulmonary syndrome, which can also manifest with dyspnea and hypoxemia but is pathophysiologically distinct from portopulmonary hypertension in that abnormal vasodilation of the pulmonary vasculature leads to intrapulmonary shunting. Portopulmonary hypertension is an established marker of adverse outcome in the post-liver transplant period with 100% mortality reported in one study among patients with mPAP ≥50 mmHg. The optimal preoperative PVR threshold used to predict elevated postoperative risk must also consider morbidity linked to prolonged transplant wait time. At present, PVR >3.0 WU is considered a strong predictor of unfavorable outcome after transplant, although PVR >2.0 WU also appears to capture potential risk.

HIV-PAH The true prevalence of HIV-PAH is not known; however, this PAH subtype is an important cause of mortality in the HIV-infected population, and prognosis in these patients is among the least favorable for all PH subgroups. There is no correlation between the stage of HIV infection and the development of PAH. By contrast, population data from the U.S. Veterans Administration database suggest a positive and inverse correlation, respectively, between CD4+ count and viral load with estimated pulmonary artery systolic pressure (ePASP) on echocardiography. An ePASP >40 mmHg in HIV-infected patients is associated with a 40% increase in all-cause mortality compared to uninfected counterparts. Although delineating patients with PAH from within this cohort and other unselected populations is not possible, there is a pressing need to understand further the role of HIV-PH in prognosis patients, particularly in endemic areas of the world.

Pulmonary Hypertension Associated with Left Heart Disease Patients with PH due to left ventricular systolic dysfunction, aortic and mitral valve disease, and heart failure with preserved ejection fraction (HFpEF) are classified in WSPH group 2. The hallmark of this PH phenotype is elevated left atrial pressure with resulting pulmonary venous hypertension. In left-sided systolic heart failure or HFpEF, even mildly elevated mPAP is associated with adverse clinical outcome. It should be noted that PH in the setting of mitral stenosis or regurgitation is an indication for surgical (or percutaneous) valve intervention. Recent data suggest that PH is common in obstructive HCM and associated with fibroproliferative remodeling of distal pulmonary arterioles even when mPAP is only mildly elevated (Fig. 294-8). In amyloid cardiomyopathy, ~75% of patients have elevated mPAP, and combined pre-/postcapillary PH is the most common hemodynamic subgroup. Regardless of the cause of elevated left atrial pressure, left atrial hypertension causes pulmonary venule sclerosis and thickening that leads to PH and, ultimately, pathogenic changes to pulmonary arterioles.

Pulmonary Hypertension Associated with Lung Disease Intrinsic lung disease is the second most common cause of PH and has been observed in both chronic obstructive pulmonary disease (COPD) and interstitial lung disease. Additionally, PH is also diagnosed in diseases of mixed obstructive/restrictive pathophysiology: bronchiectasis, cystic fibrosis, mixed obstructive-restrictive disease marked by fibrosis in the lower lung zones, and emphysema predominantly in the upper lung zones. When associated with chronic lung disease, PH is usually modest. For example, 90% of COPD patients have mPAP >20 mmHg, but an mPAP >35 mmHg is observed in only 5% of patients. Nonetheless, the subgroup of patients with primary lung disease and severe PH is challenging clinically, as extensive pulmonary arterial involvement, very low DL_{CO} on pulmonary function testing, and inhibition of normal vasoreactivity are observed and are associated with poor outcome. Sleep-disordered syndromes generally result in mild PH.

Pulmonary Hypertension Associated with Chronic Thromboembolic Disease The development of PH after chronic thromboembolic obstruction of the pulmonary arteries, termed CTEPH, is well described. The incidence of CTEPH following a single pulmonary embolic event is difficult to determine accurately, but probably is between 3 and 7% of patients. Importantly, 25% of patients with CTEPH have no history of clinical venous thromboembolism, suggesting that CTEPH may develop following a subclinical pulmonary embolism or through a diverse range of mechanisms. Obstruction of the proximal pulmonary vasculature due to webbing, stricture, or focal fibrotic occlusion signifies proximal vessel involvement. Distal pulmonary arterioles remodel by luminal narrowing or obliteration. Approximately 10–15% of patients will develop a disease very similar clinically and pathologically to PAH after resection of the proximal thrombus (Fig. 294-9). Chronic thromboembolic disease refers to patients with thrombotic pulmonary arterial remodeling and diminished exercise capacity with correlative symptoms in the absence of PH. This subtype is less common than CTEPH but requires consideration in patients with prior PE and dyspnea even if echocardiography is reassuring.

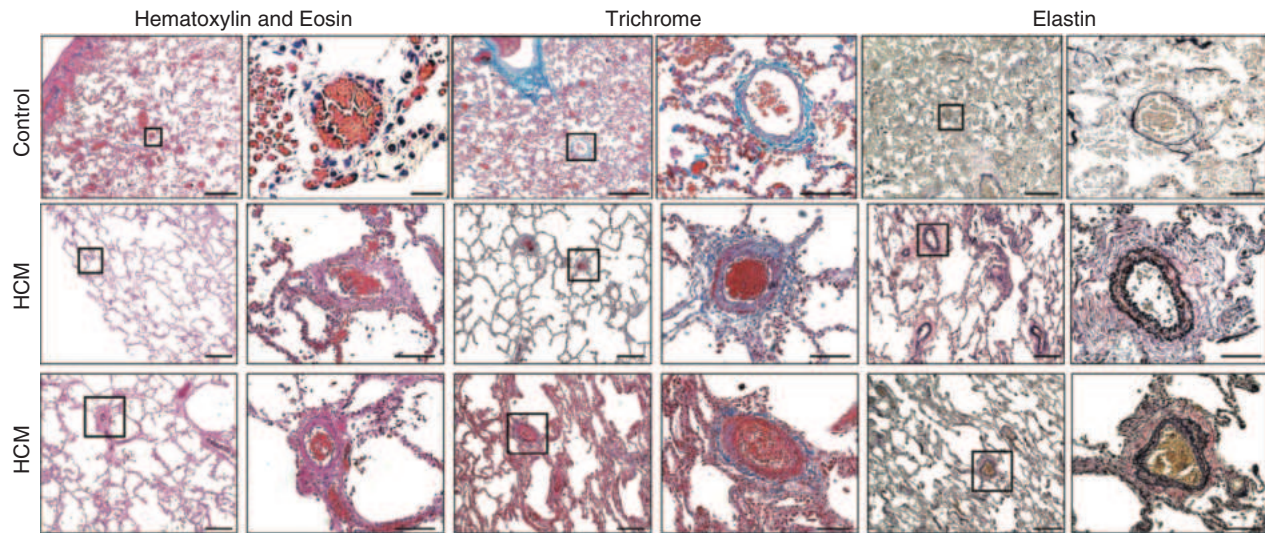


FIGURE 294-8 Pulmonary vascular remodeling in patients with obstructive hypertrophic cardiomyopathy (HCM) and mild pulmonary hypertension. Photomicrographs showing pulmonary arterial histopathophenotype of HCM. Paraffin-embedded tissue sections from control donors without lung disease and example autopsy specimens from patients with symptomatic obstructive HCM were analyzed after hematoxylin and eosin, Masson trichrome, and Verhoeff-Van Gieson staining. (Adapted with permission from BA Maron et al: *Chest* 163:678, 2023.)

■ OTHER DISORDERS AFFECTING THE PULMONARY VASCULATURE

Sarcoidosis Patients with sarcoidosis can develop PH as a result of lung involvement, and those who present with progressive dyspnea and PH require a thorough evaluation. In sarcoidosis, PH develops mainly due to granulomatous inflammation of the pulmonary vessels, although mechanical compression of pulmonary arteries by enlarged lymph nodes is also reported.

Sickle Cell Disease Cardiovascular system abnormalities are prominent in the clinical spectrum of sickle cell disease (and other hemoglobinopathies), including PH, which occurs in 6–10% of patients. The etiology is multifactorial, including hemolysis, hypoxemia, thromboembolism, chronically high CO, and chronic liver disease.

Schistosomiasis Schistosomiasis affects >230 million people worldwide, of whom 5% develop PAH. Thus, this infection is among the most common causes of PAH worldwide. The development of PAH occurs in the setting of hepatosplenic disease and portal hypertension. Indeed, even in the absence of schistosomiasis, splenectomy is a risk factor for PAH, presumably through impaired platelet sequestration and associated microthrombosis of pulmonary arterioles. Studies suggest that inflammation from a schistosomiasis infection induces pulmonary vascular injury through a combination of the following

mechanisms: luminal obstruction by worm eggs, pulmonary artery endothelial cell inflammation, or portal hypertension that promotes a portopulmonary hypertension-PH phenotype. The diagnosis is confirmed by finding the parasite ova in the urine or stool of patients with symptoms, which can be difficult. The efficacy of therapies directed toward PAH in these patients is unknown.

■ PHARMACOLOGIC TREATMENT OF PAH

There are 14 U.S. Food and Drug Administration (FDA)–approved medical therapies for PAH, and standardized treatment strategies have been developed that emphasize early, aggressive pharmacotherapy initiated at a specialty clinical center. Among optimally treated patients, the 1-, 3-, and 5-year survival estimates are 82, 67, and 58%, respectively, but this may overestimate risk since outcome data in the era of routine dual (and in some cases triple) therapy are lacking. All approved medical therapies target the prostacyclin, NO, or endothelin receptor signaling pathways. Drug delivery methods now include oral, inhaled, subcutaneous (including via surgically implanted devices), and intravenous routes.

Prostanoids In PAH, endothelial dysfunction and platelet activation cause an imbalance of arachidonic acid metabolites with reduced prostacyclin levels and increased thromboxane A₂ production. Prostacyclin (PGI₂) activates cyclic adenosine monophosphate

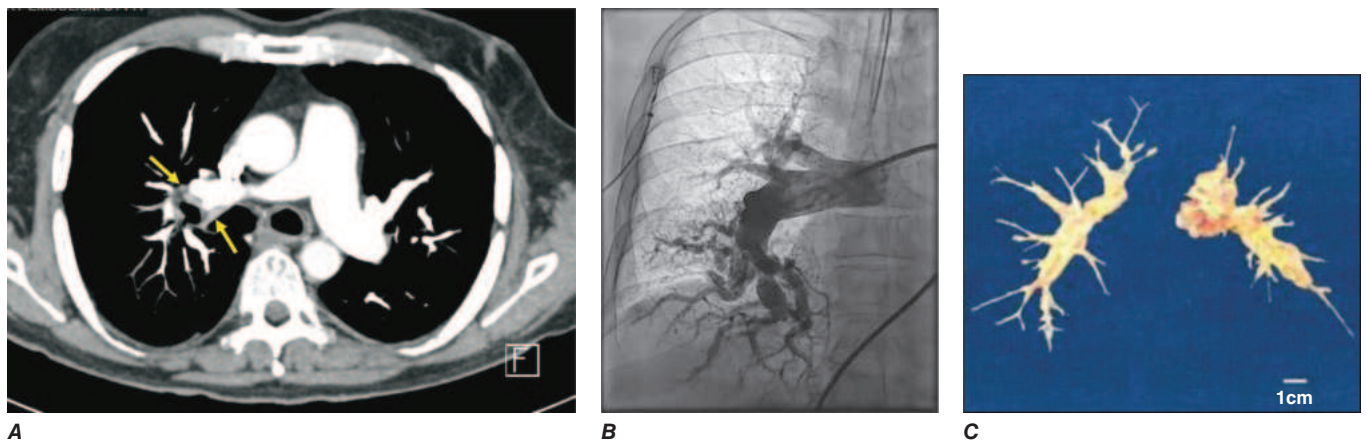


FIGURE 294-9 Chronic thromboembolic pulmonary hypertension (CTEPH) imaging findings and surgical endarterectomy specimen. **A.** Contrast-enhanced computed tomography of the chest shows an obstructive vascular pattern involving segmental pulmonary arteries (yellow arrows) in a 63-year-old man with exertional dyspnea and remote history of pulmonary embolism. **B.** Still image of a pulmonary angiography of the right lung (submaximal injection shown) shows pulmonary artery stricture, webbing, and severe debranching that is classic for CTEPH. **C.** Fibrotic, chronic clot specimens resected during surgical pulmonary endarterectomy, which is curative in most CTEPH patients. (Panel C is reproduced with permission from IM Lang, M Madani: *Update on chronic thromboembolic pulmonary hypertension. Circulation* 130:508, 2014.)

(cAMP)-dependent pathways that mediate vasodilation. PGI₂ also has antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation. Protein levels of prostacyclin synthase are decreased in pulmonary arteries of patients with PAH. This imbalance of mediators is offset therapeutically by the administration of either exogenous prostacyclin (and analogues, termed prostanoids) or a prostacyclin receptor agonist.

Epoprostenol was the first prostanoid available for the management of PAH. Epoprostenol delivered as a continuous intravenous infusion improves functional capacity and survival in PAH. The efficacy of epoprostenol in World Health Organization (WHO) Functional Class (FC) III and IV PAH patients was demonstrated in a clinical trial that showed improved quality of life, mPAP, PVR, 6-MWD, and mortality. Treprostinil has a longer half-life than epoprostenol (~4 h vs ~6 min), which allows for subcutaneous administration. Treprostinil has been shown to improve pulmonary hemodynamics, symptoms, exercise capacity, and survival in PAH. Inhaled prostacyclin provides the beneficial effects of infused prostacyclin therapy without the inconvenience and side effects of infusion catheters (e.g., risk of infection and infusion site reactions). Both inhaled iloprost and treprostinil have been approved for patients with PAH and severe heart failure symptoms. Oral prostacyclin is also efficacious in clinical trials, but the maximal dose is modest and, therefore, generally reserved as a second-line therapy.

Selexipag is an oral nonprostanoid diphenylpyrazine derivative that binds the prostaglandin I₂ (IP) receptor with high affinity. The active metabolite of selexipag has a prolonged half-life in comparison with prostanoid analogues and permits twice-daily dosing. The efficacy of selexipag was evaluated in patients with PAH in New York Heart Association (NYHA) FC II to III on background therapy with either an endothelin-1 (ET-1) receptor antagonist or sildenafil, or both. This trial represents the largest randomized placebo-controlled trial among patients with PAH ever completed, enrolling 1156 patients treated for a median of 1.4 years. Selexipag reduced the risk of hospitalization and the risk of disease progression by 43% ($p < .0001$) compared to those who received placebo. There were no significant differences in mortality between the two study groups, and the side effect profile was similar to that of prostacyclins.

Endothelin Receptor Antagonists Endothelin receptor antagonists (ERAs) inhibit the detrimental effects of ET-1, a potent endogenous vasoconstrictor and vascular smooth muscle mitogen. In PAH, ET-1 associates positively with PVR and mPAP and inversely with CO and 6-MWD. The ET-1 signaling axis is complex and cell type-specific: ET type A (ET_A) and type B (ET_B) receptors expressed in pulmonary artery smooth muscle cells mediate vasoconstriction, whereas human pulmonary artery endothelial cells express ET_B receptors that promote ET-1 clearance and vasodilation through endothelial nitric oxide synthase activation and prostacyclin release.

The three ERAs approved for use in the United States are the non-selective ET_{A/B} receptor antagonists bosentan and macitentan and the selective ET_A antagonist ambrisentan. Studies have shown that bosentan improves hemodynamics and exercise capacity and delays clinical worsening. The randomized, placebo-controlled, phase 3 Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 trial comparing bosentan to placebo demonstrated improved symptoms, 6-MWD, and WHO FC in patients treated with bosentan. The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients (EARLY) study comparing bosentan to placebo demonstrated improved PVR and 6-MWD in patients with WHO FC II.

Several studies, including the phase 3, placebo-controlled Ambrisentan in Pulmonary Arterial Hypertension, (ARIES)-1 trial, have demonstrated that ambrisentan improves exercise tolerance, WHO FC, hemodynamics, and quality of life in patients with PAH. More recently, the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) trial randomized 742 PAH patients to receive placebo or macitentan, which is an ET_{A/B} antagonist with optimized receptor binding affinity. The majority of patients were on some form of background PAH therapy. Over an average treatment duration of 85 weeks, the hazard ratio for

achieving the composite primary endpoint of PAH-related clinical worsening, which included death or disease progression, was decreased by 45% in the 10-mg dose arm.

Nitric Oxide Pathway Effectors The gaseous, lipophilic molecule NO• is generated by endothelial nitric oxide synthase in endothelial cells and activates soluble guanylyl cyclase (sGC) to generate cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells and platelets. The cyclic nucleotide cGMP is a second messenger that induces vasodilation through relaxation of arterial smooth muscle cells and inhibits platelet activation. Phosphodiesterase type 5 (PDE5) enzymes are highly expressed in lung vascular tissue (and the corpus cavernosum of the penis). The PDE5 inhibitors prevent hydrolysis (inactivation) of cGMP to maximize NO•-dependent vasodilation, serving as the basis for use of this drug class in the treatment of PH (and erectile dysfunction). The two PDE5 inhibitors used for the treatment of PAH are sildenafil and tadalafil. Both agents have been shown to improve hemodynamics and 6-MWD.

Riociguat increases bioactive cGMP by (1) stabilizing the molecular interaction between NO• and sGC, and (2) directly stimulating sGC independent of NO• bioavailability. Riociguat significantly improved exercise capacity, pulmonary hemodynamics, WHO FC, and time to clinical worsening in patients with PAH and is the sole approved pharmacotherapy for CTEPH patients for whom surgical pulmonary endarterectomy is ineffective or contraindicated.

Activin Signal Inhibitor Therapy Motivated by basic and translational data suggesting that treatment with a TGF-β ligand trap inhibits the proliferative activity of activin ligands in pulmonary vascular cells, sotatercept was developed as a novel fusion protein of the Fc domain of human IgG and the extracellular domain of activin receptor type II. Sotatercept blocks activin receptor II-ALK 4/5/7 signal transduction to upregulate BMPR2 bioactivity. The putative effect of this drug's reaction in PAH is rebalancing of the TGF-β-BMPR2 pathway to restore normal cellular survival and growth patterns.

The PULSAR trial was a large, phase 2, placebo-controlled trial demonstrating a dose-dependent decrease in PVR by sotatercept (0.3 and 0.7 mg/kg administered as an injection) at study week 24 compared to baseline of -1.8 WU and 3.0 WU, respectively. The STELLAR trial was a phase 3 placebo-controlled trial that studied the effect of sotatercept 0.3 mg/kg with target dose of 0.7 mg/kg on 6-MWD. The patients in the study had moderate or severe symptom burden despite ongoing pulmonary vasodilator treatment. In fact, ~60% of patients were on triple therapy, including 40% who were on treatment with intravenous prostacyclin treatment, typically reserved for high-risk or very-high-risk patients (see below). Despite this prior treatment, sotatercept therapy resulted in an average of +40 m improvement in 6-MWD compared to -1.4 m for placebo and was associated with significant improvement in nearly all secondary endpoints including WHO FC improvement, reduction in NT-proBNP level, and shorter time to death or PAH worsening. Telangiectasia development was observed in 10.4% of patients in the sotatercept group, which tracks with the angioproliferative bioactivity reported for TGF-β, although the clinical relevance of these vascular anomalies is not known. Finally, the long-term open-label study that tracked clinical progress up to 1 year in patients from PULSAR demonstrated a sustained (but not progressive) benefit in PVR reduction by sotatercept without an unexpected change in the proportion of side effects given the duration of the follow-up period.

■ APPROACH TO PAH TREATMENT

Treatment aims to achieve a low clinical risk profile, defined as a 1-year mortality risk of <5%. Generally, this describes a patient with minimal symptoms, WHO FC I or II, 6-MWD >440 m, and cardiac index ≥2.5 L/min per m². To accomplish this goal, early referral to an expert center is advised since most patients will ultimately require two or more PAH pharmacotherapies in addition to risk factor modification (such as a low-sodium diet), diuretic use to include mineralocorticoid receptor antagonists if tolerated, supplemental oxygen, and prescription (or supervised) exercise (Fig. 294-10). It is clear that targeting the diverse pathobiologic and pathophysiologic events involved in vascular

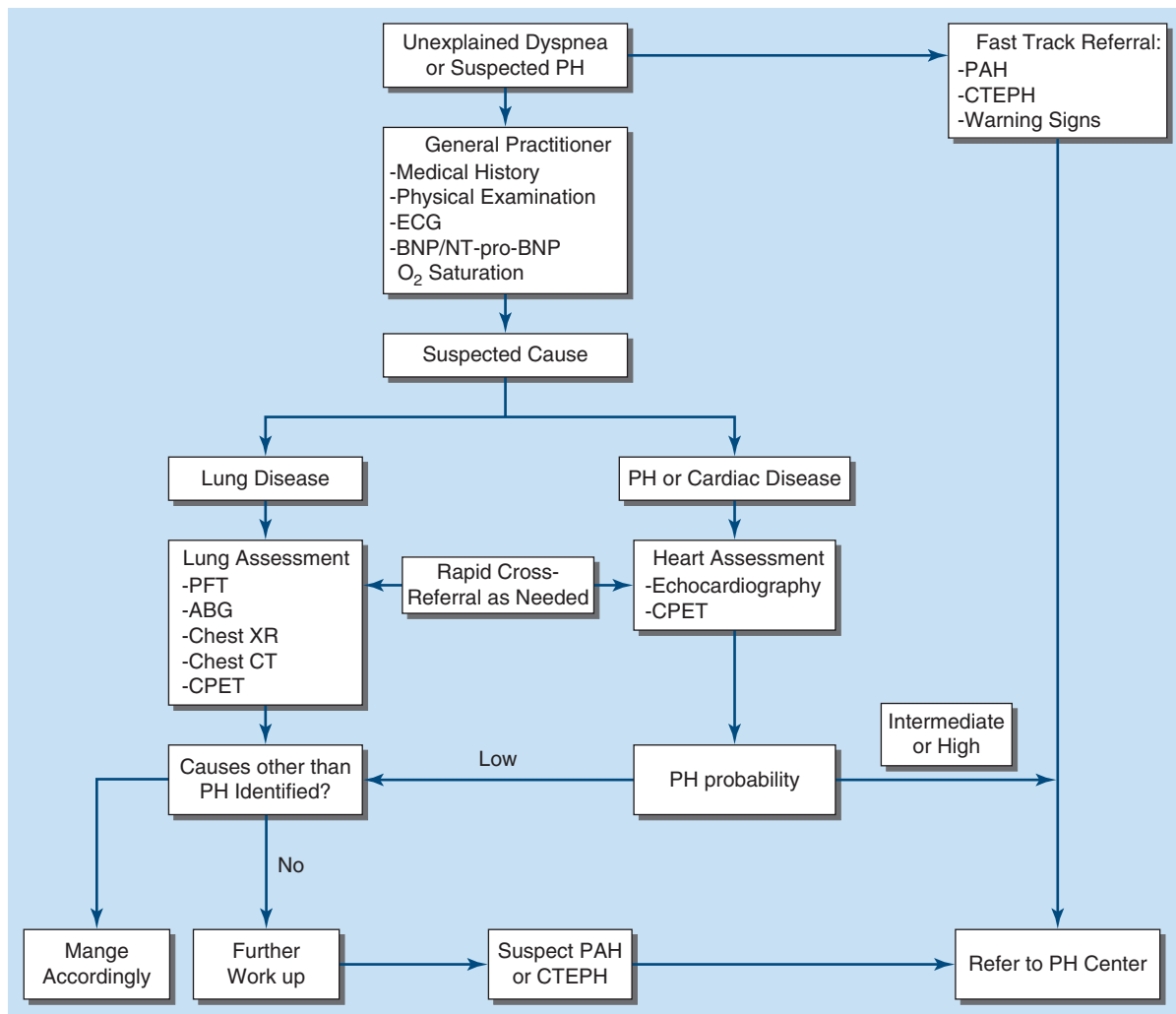


FIGURE 294-10 Strategy for diagnosing pulmonary hypertension (PH) in clinical practice. Diagnostic algorithm of patients with unexplained dyspnea and/or suspected pulmonary hypertension. ABG, arterial blood gas analysis; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PFT, pulmonary function tests; PH, pulmonary hypertension. Warning signs include rapid progression of symptoms, severely reduced exercise capacity, presyncope or syncope on mild exertion, and signs of right heart failure. Lung and heart assessment by specialist as per local practice. CT pulmonary angiography recommended if PH suspected. Includes connective tissue disease (especially systemic sclerosis), portal hypertension, HIV infection, and family history of PAH. (Reproduced with permission of the © ERS 2024: Eur Resp J 61:2200879, 2023; DOI:10.1183/13993003.00879-2022.)

remodeling is needed to optimize treatment. The concept of combination therapy in PAH is modeled after other complex diseases in which a similar approach has been effective, including HIV, cancer, and left heart failure.

The approach to therapy in a patient with incident PAH is outlined in Fig. 294-11. The role of early, aggressive therapy with combination oral treatments was addressed in the landmark Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension (AMBITION) trial. Treatment-naïve, incident PAH patients ($n = 500$) were randomized to a combination of ambrisentan and tadalafil, ambrisentan monotherapy, or tadalafil monotherapy. Up-front combination therapy with ambrisentan and tadalafil was associated with a 50% lower risk of clinical worsening (composite of death, lung transplantation, hospitalization for PAH worsening, and worsening PAH) when compared with the monotherapy groups. This difference was driven primarily by the delay in time to first hospitalization. Importantly, initial combination therapy was not associated with an increase in adverse events. Registry data suggest that patients on dual therapy with a PDE5 inhibitor plus ERA combinations alternative to the drugs studied in AMBITION also have better outcomes compared to patients treated with monotherapy, suggesting that the attendant benefit from combination therapy may not be drug specific.

The paradigm shift toward early, aggressive pharmacotherapy in PAH is expanding to up-front triple combination therapy. Clinical

studies on up-front triple therapy remain mixed, which is likely driven by challenges surrounding patient selection given the precarious balance between cumulative off-target effects occurring when multiple vasoactive drugs are initiated at the same time, frailty and limited hemodynamic reserve associated with advanced PAH, and need for aggressive treatment to mitigate severely abnormal hemodynamics or right ventricular heart failure. Generally, treatment deescalation, escalation, or class switching for patients with established PAH should be decided in partnership with a PAH clinical center of excellence.

Treatment of HFpEF Disease-specific treatments for HFpEF-PH are lacking. The focus of care should be to optimize contemporary treatment of HFpEF, including minimizing excessive salt and fluid intake while advancing SGLT-2 therapy, mineralocorticoid therapy, and diuretics, and encouraging regular exercise to promote weight loss and conditioning. Invasive PA pressure monitoring may be helpful for tracking elevation in LVEDP, detected as PH, to avert hospitalization.

Treatment of PH due to Lung Disease Inhaled iloprost improved 6-MWD on average +33 m in a placebo-controlled randomized clinical trial studying patients with interstitial lung disease and PH and moderate-to-severe exercise limitation. Although a promising future strategy for the routine management of patients, additional data are needed to confirm efficacy and clarify the criteria defining optimal patients for treatment since dosing is frequent and a substantial rate

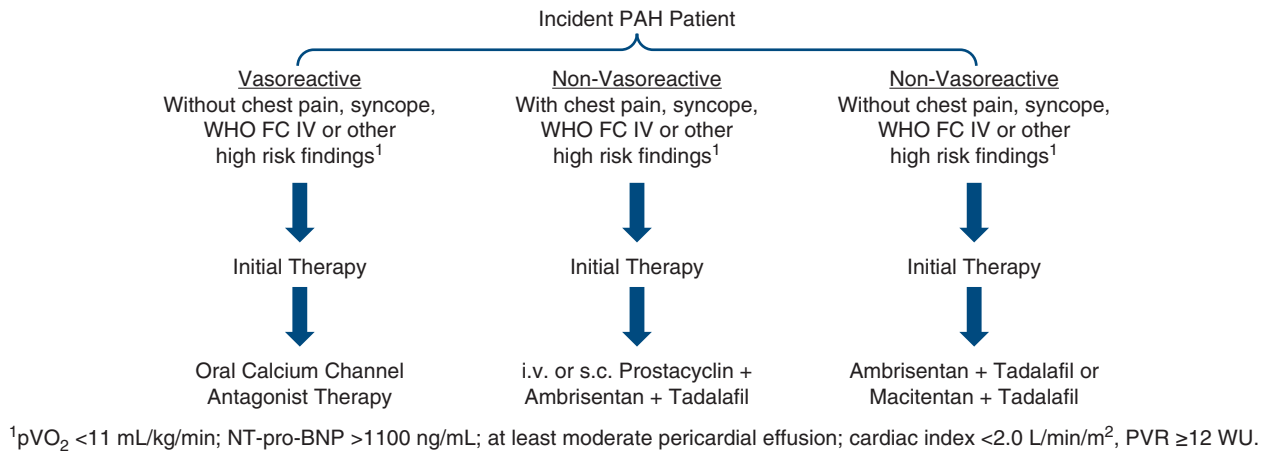


FIGURE 294-11 Treatment strategy overview for patients with newly diagnosed pulmonary arterial hypertension (PAH). Newly diagnosed patients with idiopathic, hereditary, or drug-induced PAH should be considered for vasoreactivity testing in the cardiac catheterization laboratory at an expert pulmonary hypertension center. In the absence of a high-risk clinical profile, patients who demonstrate a positive vasoreactivity response, defined by decrease in mean pulmonary artery pressure ≥10 mmHg from baseline to ≤40 mmHg without a decrease in cardiac output, should be initiated on calcium channel antagonist therapy dose titrated to optimal clinical benefit/adverse effect balance. For patients with PAH without evidence of vasoreactivity but with high-risk findings, consideration of up-front therapy with the prostacyclin analogue treprostinil administered by intravenous (IV) or subcutaneous (SC) route plus the phosphodiesterase type 5 inhibitor tadalafil and endothelin receptor antagonist ambrisentan is indicated. For patients with PAH without vasoreactivity or high-risk findings, initial combination therapy with tadalafil and ambrisentan or the alternate endothelin receptor antagonist macitentan should be considered. NT-proBNP, N-terminal pro-B-type natriuretic peptide; pVO₂, peak volume of oxygen consumption; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization Functional Class; WU, Wood units. (Reproduced with permission from BA Maron: Revised definition of pulmonary hypertension and approach to management: A clinical primer. *J Am Heart Assoc* 12:e029024, 2023.)

of treatment attrition is notable. It is also unclear if inhaled iloprost is generalizable to other lung-PH phenotypes, as at least one study focusing on COPD-PH was terminated early, presumably owing to a lack of benefit or adverse effects.

Treatment of CTEPH Pulmonary endarterectomy performed at a high-volume surgical referral center is the preferred therapy in patients with favorable anatomy and profile. Distal fibrothrombotic remodeling, PVR >12 WU, right heart failure, and NYHA FC IV are viewed

as high-risk findings and may be prohibitive in terms of postoperative risk. Patients who are ineligible for pulmonary endarterectomy or do not experience a complete clinical result in the postoperative phase should be considered for treatment with riociguat (sGC stimulator) therapy, balloon pulmonary angioplasty (BPA), or a combination of both. Compared to riociguat, BPA modulates a decrease in mPAP of −9.3 mmHg but requires on average five procedural attempts and is associated with some important potential complications, including hemoptysis and reperfusion pulmonary edema (Fig. 294-12).

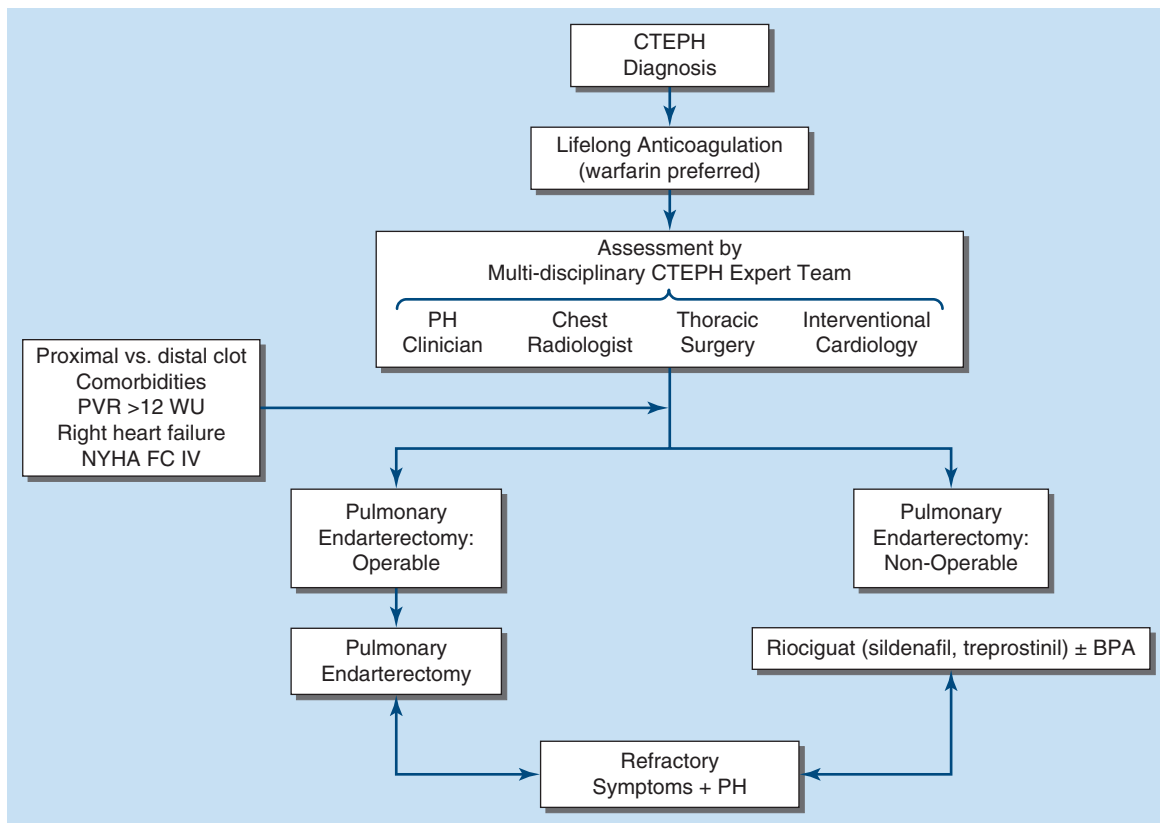


FIGURE 294-12 Algorithm for the management of chronic thromboembolic pulmonary hypertension (CTEPH). BPA, balloon pulmonary angioplasty; NYHA FC, New York Heart Association functional class; PH, pulmonary hypertension; PVR, pulmonary vascular resistance. (Adapted from NH Kim et al: *Eur Respir J* 53:1801915, 2019.)

TABLE 294-2 FDA-Approved Therapies for the Treatment of Pulmonary Arterial Hypertension (PAH)

GENERIC NAME	ROUTE OF ADMINISTRATION	DRUG CLASS	INDICATION
Epoprostenol	IV	Prostacyclin derivative	Treatment of PAH to improve exercise capacity
Iloprost	Inhaled	Prostacyclin derivative	Treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA class), and lack of deterioration
Treprostinil	IV or SC	Prostacyclin derivative	Treatment of PAH to diminish symptoms associated with exercise
Treprostinil	Inhaled	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Treprostinil	Oral	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Selexipag	Oral	Selective IP receptor agonist	Treatment of PAH to improve a composite endpoint lack of clinical deterioration
Bosentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and to decrease clinical worsening
Ambrisentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Macitentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve a composite endpoint of delay of clinical worsening
Sildenafil	Oral or IV	PDE5 inhibitor	Treatment of PAH to improve exercise capacity and delay clinical worsening
Tadalafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise ability
Riociguat	Oral	Soluble guanylyl cyclase stimulator	Treatment of PAH to improve exercise ability

Abbreviations: FDA, U.S. Food and Drug Administration; IV, intravenous; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase-5; SC, subcutaneous.

■ UNMET AND FUTURE RESEARCH NEEDS IN PULMONARY HYPERTENSION

Delayed diagnosis is a major barrier to improving outcome in PAH. Improved awareness among clinicians and patients could lead to more timely diagnosis that will affect the response to therapy and survival. At-risk patients should be referred early to a specialty center that focuses on treatment of patients with pulmonary vascular disease, which will ensure their access to state-of-the-art (multidisciplinary) care. In addition, the role of currently available drugs in early-stage disease is not known and requires further investigation (Table 294-2). The anticipated approval of sotatercept is exciting and paves a path toward the availability of the first novel drug class in PAH in nearly two decades. However, clinical trial data continue to lack information from diverse patient subgroups, suggesting that health inequity in PH remains a critical opportunity for progress.

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